

Rahul Nanchal  
Ram Subramanian  
*Editors*

# Hepatic Critical Care

An abstract graphic featuring a horizontal band of vibrant, overlapping colors (blue, green, yellow, pink, and purple) that appears to flow or ripple across the middle of the cover. This band is set against a solid dark blue background. A thin white vertical line runs through the center of the cover, passing through the colorful band.

 Springer

---

## Hepatic Critical Care

---

Rahul Nanchal • Ram Subramanian  
Editors

# Hepatic Critical Care

*Editors*

Rahul Nanchal  
Medical Intensive Care Unit  
Medical College of Wisconsin  
Milwaukee  
Wisconsin  
USA

Ram Subramanian  
Emory University  
Atlanta  
Georgia  
USA

ISBN 978-3-319-66431-6      ISBN 978-3-319-66432-3 (eBook)  
<https://doi.org/10.1007/978-3-319-66432-3>

Library of Congress Control Number: 2017960808

© Springer International Publishing AG 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by Springer Nature  
The registered company is Springer International Publishing AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

---

# Contents

## Part I Physiological Alterations in Liver Disease

<b>1 Normal Hepatic Function and Physiology</b> .....	3
Achuthan Sourianarayanan	
<b>2 Circulatory Physiology in Liver Disease</b> .....	21
Kathleen Heintz and Steven M. Hollenberg	
<b>3 Respiratory Physiology in Liver Disease</b> .....	31
Paul Bergl and Jonathon D. Truwit	
<b>4 Gastrointestinal and Hepatic Physiology in Liver Disease</b> .....	45
J. P. Norvell, Anjana A. Pillai, and Mary M. Flynn	
<b>5 Renal Physiology in Liver Disease</b> .....	53
Kai Singbartl	
<b>6 Cerebrovascular Physiology in Liver Disease</b> .....	59
Jeffrey DellaVolpe, Minjee Kim, Thomas P. Bleck, and Ali Al-Khafaji	

## Part II Manifestations of Problems and Management of the Critically Ill Patient with Liver Disease

<b>7 Definitions, Epidemiology and Prognostication of Liver Disease</b> .....	75
Jody C. Olson and Patrick S. Kamath	
<b>8 Brain and the Liver: Cerebral Edema, Hepatic Encephalopathy and Beyond</b> .....	83
Gagan Kumar, Amit Taneja, and Prem A. Kandiah	
<b>9 Cardiovascular Alterations in Acute and Chronic Liver Failure</b> .....	105
Sukhjeet Singh and Steven M. Hollenberg	
<b>10 Portal Hypertensive Gastrointestinal Bleeding</b> .....	121
Kia Saeian, Akshay Kohli, and Joseph Ahn	
<b>11 Respiratory Complications in Acute and Chronic Liver Disease</b> .....	137
Vijaya Ramalingam, Sikander Ansari, and Jonathon Truwit	
<b>12 Renal Complications in Acute and Chronic Liver Disease</b> .....	153
Constantine J. Karvellas, Francois Durand, Mitra K. Nadim, and Kai Singbartl	
<b>13 Hematological Issues in Liver Disease</b> .....	163
R. Todd Stravitz	
<b>14 Nutrition Therapy in Acute and Chronic Liver Failure</b> .....	179
Panna A. Codner, Beth Taylor, and Jayshil J. Patel	
<b>15 Bacterial Infections</b> .....	191
Michael G. Ison and Madeleine Heldman	

<b>16</b>	<b>The Liver in Systemic Critical Illness . . . . .</b>	<b>201</b>
	Tessa W. Damm, Gaurav Dagar, and David J. Kramer	
<b>17</b>	<b>Pharmacological Considerations in Acute and Chronic Liver Disease . . . . .</b>	<b>211</b>
	William J. Peppard, Alley J. Killian, and Annie N. Biesboer	
<b>18</b>	<b>Non Transplant Surgical Considerations: Hepatic Surgery and Liver Trauma . . . . .</b>	<b>233</b>
	Thomas Carver, Nikolaos Chatzizacharias, and T. Clark Gamblin	
<b>19</b>	<b>Anesthetic and Perioperative Considerations in Liver Disease (Non-Transplant). . . . .</b>	<b>255</b>
	Randolph Steadman and Cinnamon Sullivan	
<b>20</b>	<b>Liver Transplantation: Perioperative Considerations. . . . .</b>	<b>269</b>
	Mark T. Keegan	
<b>21</b>	<b>Use of Extra-Corporeal Liver Support Therapies in Acute and Acute on Chronic Liver Failure. . . . .</b>	<b>291</b>
	Constantine J. Karvellas, Jody C. Olson, and Ram M. Subramanian	
<b>22</b>	<b>Assessing Liver Function in Critically Ill Patients. . . . .</b>	<b>299</b>
	Mihir Shah and Rahul Nanchal	
	<b>Index. . . . .</b>	<b>305</b>

---

## About the Editors

**Rahul Nanchal** Dr. Nanchal is Associate Professor of Medicine and serves as the director of the medical intensive care unit and critical care fellowship program at Froedtert and the Medical College of Wisconsin. He has a special interest in the care of patients with hepatic critical illness and his research focuses on outcomes of critically ill patients.

**Ram Subramanian** Dr. Ram Subramanian is Associate Professor of Medicine and Surgery at the Emory University School of Medicine in Atlanta, USA. He is the Medical Director of Liver Transplantation and oversees the Liver Critical Care services at the Emory Liver Transplant Center. His fellowship training involved combined training in Pulmonary and Critical Care Medicine and Gastroenterology and Transplant Hepatology, with a goal to focus his clinical and research interests in the field of hepatic critical care. Over the course of his academic career, he has developed a specific clinical and research expertise in extracorporeal liver support.

---

## Part I

# Physiological Alterations in Liver Disease



# Normal Hepatic Function and Physiology

1

Achuthan Sourianarayanan

## Abstract

The liver is the body's largest internal organ. It plays a vital role in many metabolic processes. The liver has a unique vascular supply with most of its blood coming from the portal venous circulation. The distribution of the portal vein and hepatic artery (which supplies the liver), hepatic vein (which drains the liver), and bile ducts (transport out of the liver) form a unique pattern. This architectural pattern is important to keep in mind as it impacts various metabolic processes of the liver, disease occurrence, and surgical options for intervention (if required). The liver performs complex functions of synthesizing and metabolizing carbohydrates, protein, and lipids. In addition, the liver plays a significant role in modification of proteins and drugs to their biologically active form (which can be used by the body). In addition to modification, the liver is involved in detoxification and filtration of drugs out of the body. Due to the myriad processes the liver is involved in, there are no specific tests or tools that can be used to comprehensively evaluate its function.

## Keywords

Aminotransferases • Liver function • Liver anatomy • Portal circulation • Biliary system  
Lipoprotein • Ammonia • Liver histology

## Learning Objectives

1. Understand the functional and architectural anatomy of liver and the significance of hepatic vascular distribution and bile ducts
2. Physiologic and functional role of the liver in synthesis, metabolism of carbohydrates lipids and protein and also bile acid synthesis and its transport
3. Biochemical tests in evaluation of liver function, abnormalities and their limitations

## 1.1 Introduction

The liver is situated between the portal and general circulation, receiving blood supply from nearly all of the organs of the gastrointestinal tract prior to this blood entering the systemic circulation. It has an important function of extracting nutrients from the gastrointestinal tract and metabolizing various agents absorbed through the gut before delivering them to the systemic circulation. The liver also has a unique role of modulating many agents absorbed from the intestinal tract thereby decreasing the agent's toxicity to the body. The liver is constantly exposed to many immunologically active agents in this process and maintains an immunological balance. In this regard, the liver operates as a complex organ with various functions which cannot be evaluated by a single test. The liver has a complex arrangement of portal circulation from the gut along with a systemic arterial supply and drainage into the systemic circulation. Also, the liver has a

A. Sourianarayanan, M.D., M.R.C.P.  
Department of Medicine, Medical College of Wisconsin, 9200 W  
Wisconsin Ave., 4th Floor FEC, Milwaukee, WI 53226, USA  
e-mail: [asourianar@mcw.edu](mailto:asourianar@mcw.edu)

biliary system which drains metabolic products into the intestinal tract. This complex anatomical architecture has significance in many diseases and surgical options. Since the liver is a vital metabolic organ, it is susceptible to various conditions that can affect any one of its many functions, which can potentially lead to critical illness.

## 1.2 Anatomy

The liver is the largest organ in the body. It is situated in the right upper quadrant of the abdomen, just below the diaphragm. It extends superiorly to the fifth intercostal space at the midclavicular line and inferiorly to the right costal margin. Laterally, it extends from the right abdominal wall to the spleen on the left side. The liver weighs about 1400 g in women and 1800 g in men, approximately 2.5% of adult body weight [1–4].

The liver is surrounded by other organs and structures, such as the diaphragm, the right kidney, the duodenum, and the stomach. These structures make indentations on the liver surface. Fissures are deeper grooves in the liver and are formed when extrahepatic vessels pass through the liver during its developmental stages. The umbilical fissure contains the umbilical portion of the left portal vein, the ductus venosus (ligamentum venosum), and the umbilical vein (ligamentum teres). A fibrous capsule (Glisson's capsule) covers the liver and reflects onto the diaphragm, adjoining these structures. This connective tissue continues as parietal peritoneum. This capsule also covers the vessels in the umbilical fissure and forms a ligamentous structure (falciparum ligament). The falciparum ligament, Glisson's capsule and its extension to the diaphragm, and the round ligament hold the liver in position. Anatomically, the falciparum ligament divides the liver into right and left lobes while surrounding the quadrate lobe of the liver [5].

There are several variations in the gross anatomy and topography of the liver. Blood vessels (hepatic artery and portal vein), lymphatics, nerves and bile ducts enter and leave the liver at the porta hepatitis. The capsule of the liver covers these structures, forming the hepatico-duodenal ligament. The hepaticoduodenal ligament covers the portal vessels and ducts, following them to their smallest branches.

### 1.2.1 Surgical/Functional/Segmental Anatomy

The falciparum ligament and umbilical fissure divide the liver anatomically into right and left lobes. This division does not correspond to the distribution of blood vessels and bile ducts, and has bearing on surgical resection. The liver can be divided into right and left (hemi-livers) based on

blood supply and duct drainage. The right hemi-lobe of the liver comprises about 50–70% of the liver mass. The liver can be further divided into segments (eight in number) based on the divisions of the portal vein, hepatic artery and bile ducts (Fig. 1.1). This division helps in surgical intervention, allowing sparing of neighboring segments and maintaining hepatic function [5, 6].

### 1.2.2 Blood Flow

The liver receives blood through the portal vein and hepatic artery, which enter at the porta hepatis. Hepatic veins drain the liver into the inferior vena cava (IVC) (Fig. 1.2).

#### 1.2.2.1 Portal Vein

The portal vein is the main source of nutrients to the liver. It carries 75–80% of the (hepatic) blood supply and approximately 20–25% of oxygen to the liver [7, 8]. The portal vein is formed by the confluence of splenic and superior mesenteric veins, behind the neck of pancreas. The splenic vein drains the short gastric, pancreatic, inferior mesenteric, and left gastroepiploic veins. The portal vein drains blood from the entire digestive tract, spleen, pancreas, and gallbladder. Blood flow to any of these areas also affects venous return and liver blood supply. Due to its close anatomic proximity, the splenic vein can be anastomosed to the left renal vein, forming a spleno-renal shunt and resulting in the drainage of gastro-esophageal varices [3, 9].

#### 1.2.2.2 Hepatic Artery

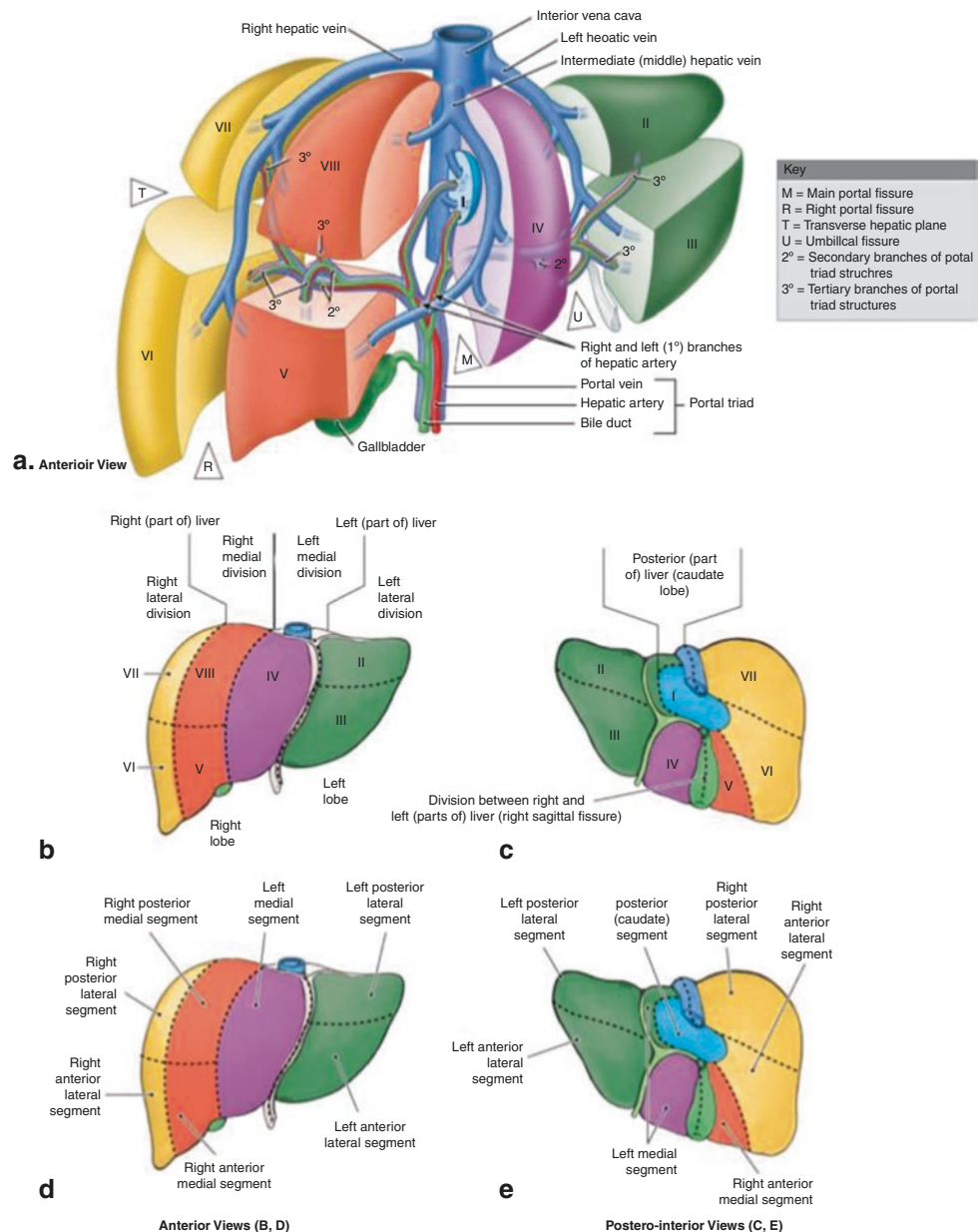
The common hepatic artery is the second branch of the celiac axis [10]. It gives off two branches, the left and right hepatic arteries, which supply the left and right hemi-livers respectively. These arteries can be further divided into two branches each. The right hepatic artery supplies the right anterior and posterior sections, while the left hepatic artery supplies the medial and lateral sections. The quadrate lobe of the liver, which extends between the gallbladder fossa and umbilical vein is supplied by the middle hepatic artery. The middle hepatic artery can arise from either the right or left hepatic artery. The cystic artery is a branch of the right hepatic artery. The superficial branches supply the peritoneal surface of the gallbladder. The deep branches supply the gallbladder and adjoining liver tissue [11].

There are extensive communications between smaller branches of the right, middle and left hepatic arteries. These communications and variations in the hepatic artery have implications on segmental resection of the liver [10, 12].

#### 1.2.2.3 Hepatic Vein

Hepatic veins drain the liver into the IVC. There are three main hepatic veins: the right, middle and left hepatic veins.

**Fig. 1.1** Anatomy of liver and its division. Reprinted with permission from Abdomen In: Agur AMR, Dalley II AF, editors, Grant's Atlas of Anatomy 14th ed. Philadelphia: McGraw-Hill; 2017



In 65–85% of individuals the left and middle hepatic vein unite before entering the IVC [13]. The caudate lobe of the liver is usually drained by one or two small veins directly into the IVC. Due to this distribution, diseases involving the hepatic veins, including thrombosis or obstruction, usually spare the caudate lobe with compensatory hypertrophy. In patients with portal hypertension, there could be communication between branches of different hepatic veins [14].

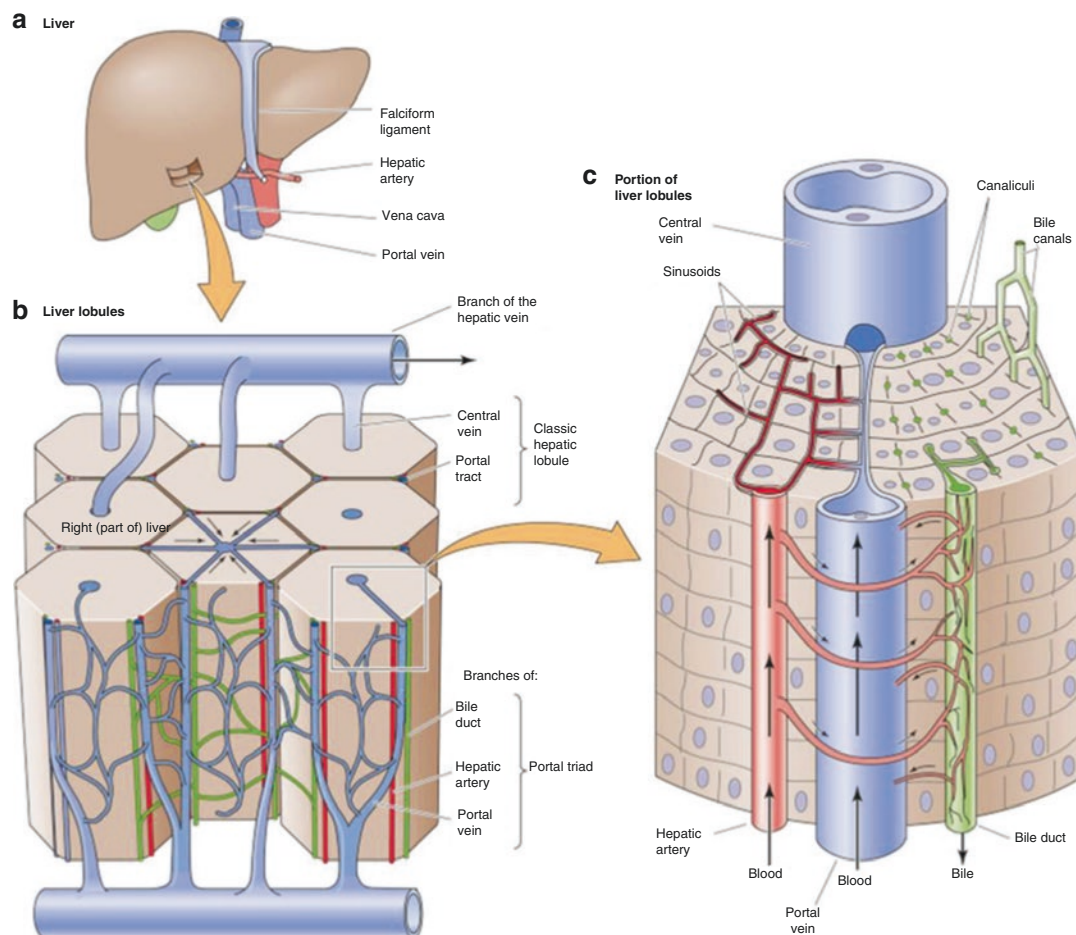
#### 1.2.2.4 Other Circulation of Relevance to Liver and Liver Diseases

The portal vein (which drains most of the abdominal organs) is the predominant vascular supply of the liver, interacting and anastomosing with the systemic circulation at different

points [15, 16]. These communicating site between the portal and systemic circulation include: esophageal submucosal venous plexus, para-umbilical veins, spleno-renal shunts and rectal submucosal venous plexus [15, 16]. These communications become significant when there is increasing pressure in the portal circulation, forming collaterals which have an increased tendency to bleed. In patients with portal hypertension, there could also be an intrahepatic communication between branches of portal veins and hepatic veins [17].

#### 1.2.2.5 Lymphatic Vessels

Lymphatic drainage of the liver is divided into superficial and deep networks. The deep networks run parallel to the portal and hepatic veins. Nearly 80% of the hepatic lymphatic



**Fig. 1.2** Blood supply to the liver. Reprinted with permission from Suchy F. Hepatobiliary Function. In: Boron W, Boulpaep E, editors. Medical Physiology. 3rd ed. Philadelphia: Elsevier; 2017

network drains along portal tracts and into hepatic nodes near the porta hepatis. Lymphatic vessels adjacent to hepatic veins drain into lymph nodes near the vena cava [18].

### 1.2.3 Nerves

The liver is innervated by both sympathetic and parasympathetic nerves. These nerves arise from the lower thoracic ganglia, celiac plexus, vagus nerve, and the right phrenic nerve. The nerves form a plexus around portal vein, hepatic artery and bile duct, entering the liver through the hilum. The arteries are innervated by sympathetic nerves, whereas the bile ducts are innervated by both parasympathetic and sympathetic nerves [19].

### 1.2.4 Bile Ducts

The biliary system includes both intrahepatic and extrahepatic ducts, ranging in size from ductules (which are less

than 0.02 mm in diameter) to large ducts (0.4–12 mm in diameter) [20]. Each hepatic segment is drained by a segmental bile duct, which drains into the right or left hepatic duct (corresponding to right or left hemi-livers, respectively). These hepatic ducts form the common hepatic duct. The common hepatic duct forms common bile duct with addition of cystic duct from the gall bladder [21]. The common bile duct enters the second part of the duodenum through the sphincter of Oddi. The sphincter of Oddi has both circular and longitudinal muscle and is affected by cholecystokinin and controls the release of bile [22]. The gallbladder is where bile is concentrated and receives up to 1 l of bile per day. Bile is released following stimulation mediated by cholecystokinin.

Many liver diseases affect intrahepatic ducts, resulting in chronic liver disease and cirrhosis. Primary biliary disease and primary sclerosing cholangitis are mediated by immune reaction, involving bile ducts of different sizes. Primary sclerosing cholangitis could involve both large or small intrahepatic ducts and extrahepatic ducts [3].



### 1.3 Function

The liver is an important site of lipid, carbohydrate and protein synthesis and its metabolism. It is also involved in body's immunological process, synthesis and transport of bile and metabolism of various agents including drugs [23].

#### 1.3.1 Lipid Metabolism

Lipoprotein and lipids are important for cell metabolism and synthesized in liver.

**Lipids:** Lipids are metabolized predominantly in the liver, existing in the body as cholesterol, triglycerides and phospholipids. Cholesterol is an important component of the cell membrane. Cholesterol is also a precursor for many steroid hormones and bile acids. The liver is an important site of cholesterol synthesis, which also occurs in nearly all tissues. In the liver, cholesterol can be derived from chylomicron remnants, which are absorbed from the intestine by lysosomes. Cholesterol is also synthesized from acetyl co-enzyme A in hepatic microsomes and by the enzyme 3-hydroxy-3-methylglutaryl-coenzyme-A reductase in cytosol. The 3-hydroxy-3-methylglutaryl-coenzyme-A reductase enzyme is present in peri-portal cells where most of the cholesterol synthesis occurs [24]. Cholesterol synthesis is increased by certain medications (cholestyramine, steroids), biliary obstruction, and terminal ileum resection. Cholesterol synthesis is reduced by medications (statins, nicotinic acid), increased bile acids, and fasting [25]. Triglycerides are free fatty acids attached to a glycerol base. They are involved in transporting fatty acids from the intestine to the liver and other tissues. Triglycerides act as an energy store. Phospholipids have one or more phosphate groups (choline or ethanolamine) in addition to fatty acids on a glycerol base. Phospholipids are an important component of all cell membranes.

**Lipoprotein:** Lipoproteins are composed of apolipoprotein, phospholipids and cholesterol. There are different lipoproteins, differentiated by density and associated apolipoproteins. Lipoproteins are hydrophilic on the outside and hydrophobic on the inside. Lipoproteins are involved in transporting lipids in the plasma as well as metabolism [26]. Lipoproteins are essential in transporting lipids absorbed from the intestine (chylomicrons) and lipids that have been endogenously synthesized (VLDL, LDL, HDL) [4].

**Liver diseases:** Total and free cholesterol levels are increased in patients with cholestatic liver disease. In subjects with primary biliary cirrhosis, cholesterol levels are elevated without any increased risk for coronary artery dis-

ease [27]. Patients with severe malnutrition and decompensated cirrhosis have reduced serum cholesterol. Triglyceride elevation is seen in patients with alcoholic fatty liver disease [28]. Certain medications can result in liver parenchymal injury by reducing apolipoprotein synthesis and causing reduction of triglyceride export, which increases hepatic steatosis.

#### 1.3.2 Carbohydrate Metabolism

The liver has an important role in carbohydrate metabolism. In a fed state, glycogen synthesis occurs preferentially in zone 3 (peri-venous) hepatocytes. In a fasting state, glycogenolysis and gluconeogenesis occur in zone 1 (peri-portal) hepatocytes [29] (Table 1.1). After glycogen stores have been replenished, excess glucose may be converted to lactate. Lactate can again be used as a substrate in gluconeogenesis by peri-portal hepatocytes. The liver is also the site of fructose and galactose metabolism [30].

**Liver disease:** In patients with cirrhosis, there is a reduction in energy production from carbohydrates during a fasting state. Reduced glycogen reserves and impaired release of glucose from the liver may be related to this discrepancy. In patients with acute liver failure, a marked reduction in carbohydrate synthesis results in low serum glucose levels. In cirrhosis, a relative insulin resistance is seen, with impaired glucose tolerance tests. Galactose tolerance tests, which are independent of insulin secretion, can also be used to evaluate hepatocellular function and as a measure of hepatic blood flow.

**Table 1.1** Functional heterogeneity of liver hepatocytes in their metabolic activity [29]

	Zone 1	Zone 3
Carbohydrates	Gluconeogenesis	Glycolysis
Proteins	Albumin, fibrinogen synthesis	Albumin, fibrinogen synthesis
Lipogenesis	–	++
Bile formation		
Bile salt dependent	++	–
Non-bile salt dependent	–	++
Ammonia metabolism: glutamine synthetase	–	+
Oxygen supply	+++	+
Damage following alcohol, anoxia and drugs	–	++
Cytochrome P450	+	+
After phenobarbital	+	+++++
Glutathione	++	–

### 1.3.3 Protein Metabolism

#### 1.3.3.1 Amino Acid Metabolism

Amino acids from diet and tissue breakdown enter the liver through the portal vein. They enter hepatocytes through the sinusoidal membrane [31]. Amino acids are then transaminated or deaminated to keto acids by many pathways, including Kreb's citric acid (tricarboxylic acid) cycle. Intestinal bacteria metabolize protein in the gut, converting it to ammonia. Ammonia enters the liver through the portal vein, where it is metabolized to urea by the Krebs-Henseleit cycle in peri-portal cells by mitochondria. Any excess ammonia is converted to glutamine in the peri-central hepatocytes.

Liver diseases: Kreb's cycle dysfunction occurs in acute liver failure, with associated formation of excess glutamine from ammonia, resulting in cerebral edema.

### 1.3.4 Protein Synthesis

Plasma proteins are produced in rough endoplasmic reticulum of ribosomes in hepatocytes [32]. These hepatocytes are involved in the synthesis of many proteins, including albumin,  $\alpha_1$ -antitrypsin,  $\alpha$ -fetoprotein, prothrombin, and  $\alpha_2$ -microglobulin. Hepatocytes also synthesize acute phase reactants, such as fibrinogen, ceruloplasmin, complement components, haptoglobin, ferritin and transferrin. The liver responds to cytokines, maintaining adequate acute phase response, despite progression of chronic liver disease and these levels may remain normal despite cirrhosis [33, 34].

Albumin is one of the most important plasma proteins synthesized by the liver. Approximately 12–15 g of albumin is synthesized daily to maintain an average albumin pool of 500 g. Cirrhotic patients may only be able to synthesize 4 g per day, resulting in reduced serum albumin levels. Following an acute liver injury, serum albumin levels may not decrease, as the half-life of albumin is about 22 days. Hence, serum albumin levels may not be reflective of disease severity [35–38].

Ceruloplasmin is a copper binding glycoprotein that contains six copper atoms per molecule. It is present in low concentrations in patients with homozygous form of Wilson's disease [39].

Transferrin is an iron transport protein, which is inversely related to body iron status. It is important in delivering iron in its ferric state to the cell membrane. Ferritin is an acute phase reactant involved in storing iron [40, 41].

$\alpha$ -Fetoprotein is a glycoprotein that is a normal component of the human fetus.  $\alpha$ -Fetoprotein is present in smaller concentrations after birth, but increases in patients with hepatocellular carcinoma. It is also elevated in patients with chronic hepatitis, particularly viral hepatitis.

Anti-coagulation and pro-coagulant factors are synthesized in liver. The liver synthesizes all anti-coagulation factors, except von-Willebrand factor and factor VIIIc. This includes both vitamin K dependent factors, such as factors II, VII, IX and X, and non-vitamin K dependent factors V, VIII, XI and XII, fibrinogen and fibrin stabilizing factor XIII. Pro-coagulation factors synthesized in the liver include anti-thrombin III (ATIII), protein C, protein S, and heparin co-factor II. Hence, bleeding or thrombotic states can be found in liver disease [42–44].

Complement components (C3) tend to be reduced in patients with cirrhosis. C3 is also low in alcoholic cirrhosis or acute liver failure, likely due to reduced synthesis by liver. Complement C3 can however be increased in primary biliary cirrhosis without cirrhosis [45].

Other proteins synthesized by the liver include,  $\alpha_1$  globulins,  $\alpha_2$  globulins,  $\beta$  globulins and  $\gamma$  globulins, glycoproteins and hormone binding globulins. They are reduced in chronic liver disease, similar to serum albumin, due to reduced synthesis. Nearly 90% of  $\alpha_1$  globulins are  $\alpha_1$  antitrypsin. Its reduction can correspond to antitrypsin deficiency disorder.  $\alpha_1$  antitrypsin is synthesized in the endoplasmic reticulum of the liver. Deficiency results in unopposed action of trypsin and other proteases with resultant damage of target organs (lung and liver). Reduction in  $\alpha_1$  antitrypsin is seen in those with mutation for  $\alpha_1$ -antitrypsin gene. The  $\alpha_2$  globulins and  $\beta$  globulins include lipoprotein, which correlate with serum lipid levels in liver diseases.  $\gamma$  globulins are usually elevated due to increased production in liver disease, especially in cirrhosis [25, 41].

Immunoglobulins (IgM, IgG and IgA) are synthesized by B cells of the lymphoid system. A non-specific increase in all levels of immunoglobulins can be seen in patients with cirrhosis in response to bacteremia. Specific immunoglobulins can relate to certain chronic liver diseases. An increase in IgG levels is seen in autoimmune liver disease. IgM elevation is found among patients with primary biliary cirrhosis. In alcoholic liver disease, IgA levels can be elevated. Cholestatic diseases associated with large bile duct obstruction can also have increased immunoglobulin levels [46].

### 1.3.5 Bile Synthesis and Transport

Bile acids are synthesized predominantly in the liver [47, 48]. They are present as bile acids (primary and secondary) and bile salts. The primary bile acids (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol. This synthesis occurs by either  $7\alpha$  hydroxylation of cholesterol in the liver or by  $27\alpha$  hydroxylation of cholesterol in many body tissues, including endothelium. Bile acid synthesis is mediated by cytochrome P450 enzymes [49]. Once synthesized, bile acids are conjugated with amino acids (taurine or

glycine) to form bile salts. Bile salts are excreted into the biliary canaliculus against a concentration gradient through a bile salt export protein. The bile salts then enter the intestinal lumen where they are subsequently sulphated or glucuronated and excreted through stool. In the intestinal lumen, the primary bile acids are converted into secondary bile acids (deoxycholic acid and lithocholic acid) by colonic bacteria [50].

In a given day, 4–6 g of bile acids are synthesized and 250–500 mg are lost in stool. Bile salts are stored in the gallbladder and released into the small bowel with meals. Conjugation of bile acids facilitates intraluminal concentration and improves digestion and absorption of fat from intestinal lumen. Conjugated bile acids form micellar and vesicular associations with lipids in the upper intestine and facilitates lipid absorption. Nearly 95% of bile salts are absorbed in the terminal ileum and proximal colon by active transport processes. Bile salts then pass through the portal circulation and are absorbed into the liver through the basolateral membrane of hepatocytes. Bile salts are then re-conjugated and re-excreted into bile. In a given day there may be 2–12 enterohepatic circulations [50, 51].

Serum bile salt concentration depends on many factors, including hepatic blood flow, hepatic bile uptake, intestinal motility and its bile salt secretion [52]. Altered bile salt excretion is relevant in onset and progression of gallstones and steatorrhea. Cholestatic liver disease is associated with decreased intrahepatic metabolism of bile salts. In small bowel bacterial overgrowth, there is increased bile acid de-conjugation, which results in excess intestinal absorption of free bile acids. The corresponding decrease in intestinal bile acids and presence of de-conjugated bile acids, which are less efficient in fat absorption, results in steatorrhea. The free bile acids that have been absorbed enter the entero-hepatic circulation. Terminal ileum resection interrupts enterohepatic circulation, and bile acids are not absorbed. These bile acids are lost in stool, causing diarrhea and an overall reduction in systemic bile acid [53].

### 1.3.6 Immunological Function

The liver has significant immunologic function, despite not being a classic lymphoid organ, such as the thymus, spleen or lymph nodes. Nearly one-third of hepatic cells are diverse, non-parenchymal cells. They include biliary cells, liver sinusoidal endothelial cells (LSEC), Kupffer cells (KC), stellate cells, and intrahepatic lymphocytes. The lymphocytes predominantly reside in the portal tract but are also scattered throughout the liver parenchyma. The liver is also an important organ in immune modulation and development of immune tolerance to different antigens from the gut and other parts of the body [54].

The lymphocytes present in liver include traditional T and B cells, which are involved in adaptive immunity, along with natural killer (NK) and natural killer T (NKT) cells that are involved in innate immunity. NK cells represent nearly 20–30% of the total number of lymphocytes in the liver, compared to <5% of lymphocytes seen in peripheral blood [54, 55]. NK cells are usually involved in innate immunity but can also be involved in adaptive immunity. NK cells acquire antigen specific receptors and produce long-lived memory cells. In a similar manner, NKT cells play an important role in regulating innate and adaptive immunity, mediated through a variety of cytokines. Through many diverse mechanisms, NKT cells are involved in liver injury-mediated inflammatory regeneration and fibrosis. The liver is unique with the presence of certain antigen presenting cells, such as LSEC, KC, and hepatic dendrite cells. LSEC and KC predominantly reside in liver sinusoids and hepatic dendrite cells reside in the portal triad and around central veins. These antigen-presenting cells scan for antigens (both conventional and non-conventional) and are involved in immune recognition and tolerance. The increased exposure to antigens from the digestive tract increases risk of over activation of the immune system, which could potentially have harmful consequences to the body. The liver also plays an important role in immune tolerance, to these antigens and also having the ability to switch from a tolerant to responsive immune state [54].

---

## 1.4 Histology and Microanatomy

### 1.4.1 Histological Assessment/Biopsy

Liver biopsy is usually performed percutaneously, between the right intercostal spaces or by subcostal costal approach, under ultrasound guidance. The sample obtained per pass is usually small, 1/50,000 of total liver size [56]. Liver tissue can also be obtained by transvenous approach, which is associated with a decreased risk of bleeding. In this approach, pressure measurements from hepatic vein and portal vein can be assessed. This approach can give a better assessment of liver disease but has the disadvantage of obtaining smaller samples for tissue analysis.

### 1.4.2 Liver Normal Histology

Normal liver histology consists of portal tracts, terminal hepatic venules and liver parenchyma. The portal tract contains the hepatic artery, portal vein, biliary ducts, nerves, and connective tissue stroma that the portal structures are en-sheathed in. The portal tracts are separated by liver parenchyma, which consists of plates of hepatocytes with



sinusoids between them. The hepatocytes are arranged in single cell plates separated by sinusoids. Terminal hepatic venules are present in the midst of hepatocellular plates and are equidistant from portal tracts (Figs. 1.3 and 1.4). The connective tissue around the portal tracts also have a number of macrophages, lymphocytes, and other immunologically active cells [57].

#### 1.4.2.1 Hepatocytes

Hepatocytes are the predominant cells in liver tissue and constitute nearly 60% of the liver cell population, occupying 80–90% of liver volume [8]. They are polyhedral cells arranged in single cell plates separated by sinusoids on either side. The hepatocytes are connected on their lateral sides to each other and have sinusoidal on other two sides. On its lateral wall there are canalicular domains, which form tight junction with adjacent hepatocytes to form bile canaliculi. The canaliculi drain into portal tracts. There are numerous microvilli on its sinusoidal surfaces, facilitating absorption and filtration of particles [57].

#### 1.4.2.2 Endothelial Cells and Sinusoids

The sinusoids are covered by endothelial cells and form the extravascular space of Disse. The endothelial cells have fenestrations, which allow material to pass and help in absorption and filtration. The material filtered through endothelial cells is dependent on the size of the particle, in relation to the fenestrations, and the charge of the particle [58].

#### 1.4.2.3 Biliary Ducts

Bile canaliculi are formed from adjacent hepatocytes by a tight junction, emptying into bile ducts through the canal of Hering. They are present in the connective tissue stroma in the portal triad, along with hepatic artery and portal vein. Bile canaliculi are supplied by terminal branches of the hepatic artery within the portal tract [59].

#### 1.4.2.4 Stellate Cells

Stellate cells (Ito cells) are located in the space of Disse and store vitamin A and fat. However, when activated, these cells can be transformed to myofibroblast-like cells and promote fibrosis [60].

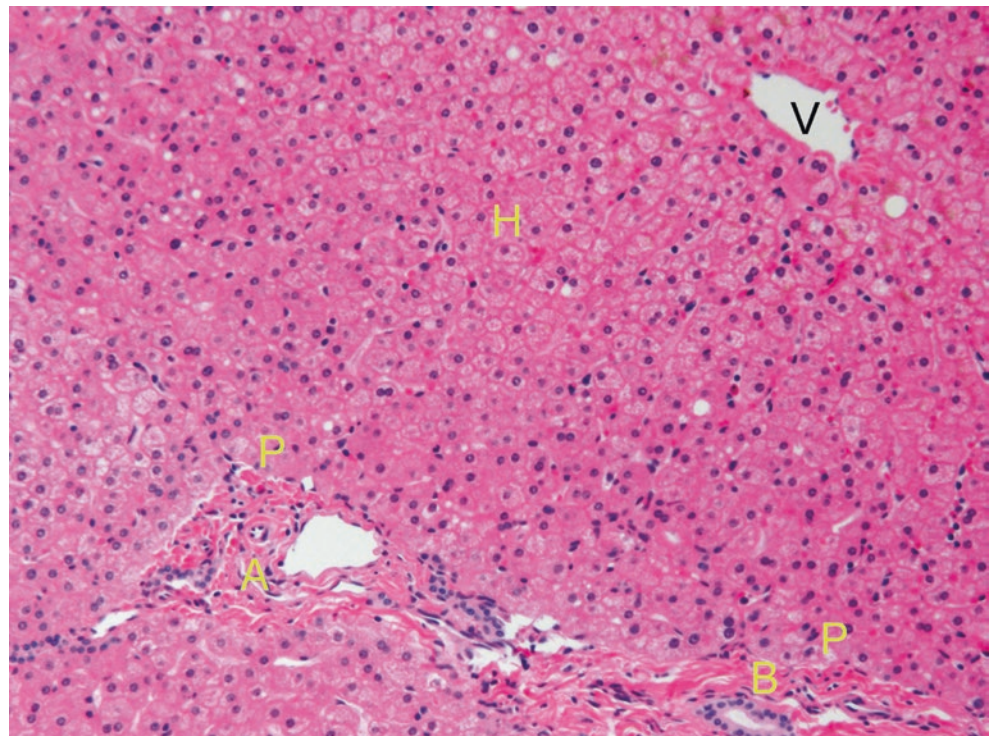
#### 1.4.2.5 Macrophages

Kupffer cells and other macrophages are involved in various responses to injuries, toxic exposure, and infectious agents [61].

### 1.4.3 Architecture of the Liver

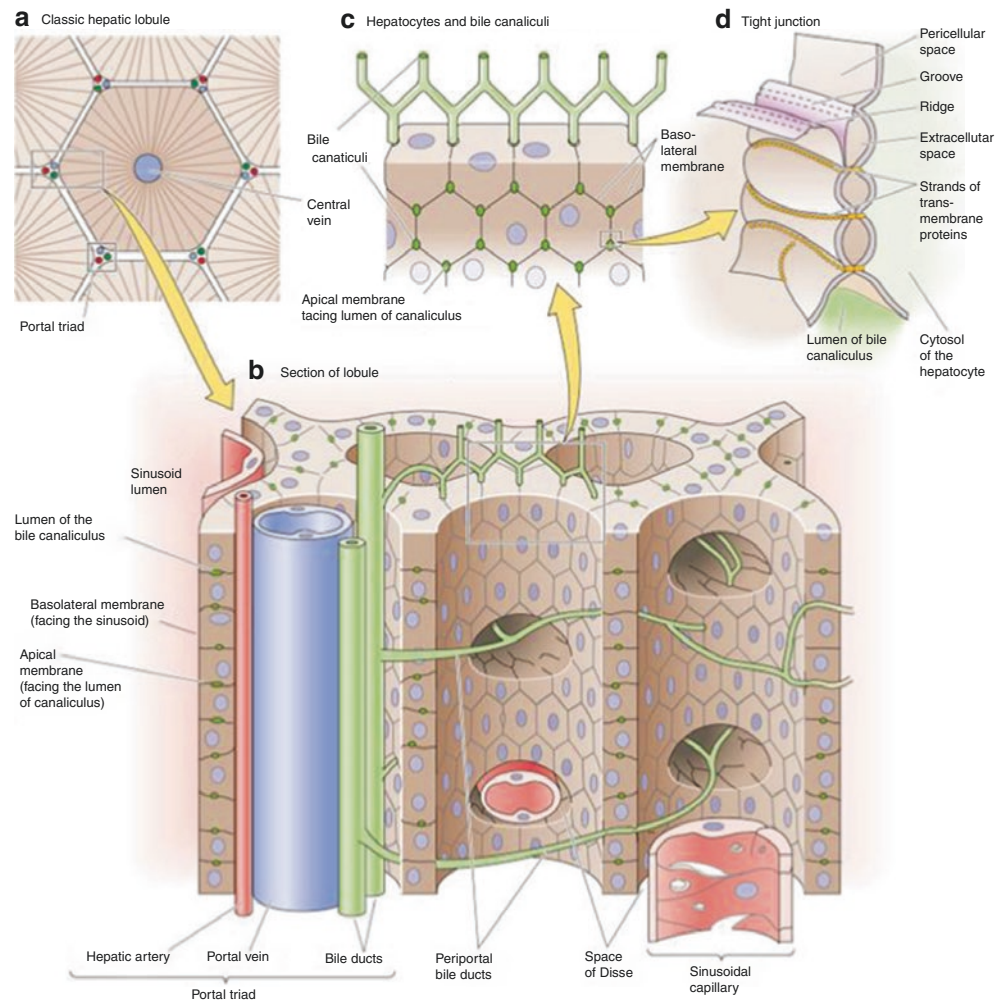
The architecture of hepatocytes, blood vessels, and bile ducts can be categorized by lobules or acini. A lobule is a hexagon with a single hepatic vein at its center and six portal triads at its periphery, supplying blood and nutrients to the liver parenchyma in between. The acinus nodule is a small group of hepatic parenchyma cells centered around the terminal hepatic artery, portal vein or alongside other structures present in the portal triad. Hence, the simple liver acinus can lie

**Fig. 1.3** Liver microanatomy. A hepatic artery; B bile ducts in portal tracts; H hepatocytes arranged as single row between portal tracts and central vein; P portal tracts; V central vein (Photomicrograph courtesy: Dr K Oshima MD, Associate professor, Department of pathology, Medical college of Wisconsin, Milwaukee, WI)





**Fig. 1.4** Histological architecture of liver. Reprinted with permission from Suchy F. Hepatobiliary Function. In: Boron W, Boulpaep E, editors. Medical Physiology. 3rd ed. Philadelphia: Elsevier; 2017



between two or more terminal hepatic venules, with the vascular and biliary access inter digitate [62]. The portal vein, hepatic arteries, and biliary ducts that supply adjacent lobules and acini can extend to different lobules. The zone near the hepatic artery and portal vein has higher blood supply and oxygenation compared to the area furthest away (near hepatic vein). Based on blood flow, acini are divided into zones 1–3. Zones near the hepatic artery and portal vein are labeled as zone 1. Zone 3 is comprised of the area farthest away and with least blood supply. The acinus is thus a physiologically functional unit. The hepatocytes in each zone, based on acinus, can be present in adjacent lobules and have sickle-cell shaped architecture [3, 62] (Figs. 1.4 and 1.5).

The acinar nodule is involved in metabolic processes, such as gluconeogenesis, glycolysis, ammonia metabolism, and bile acid synthesis. The metabolic processes occurring in liver are related to blood supply and oxygenation, based on zonal distribution (Table 1.1). This acinar modal helps in understanding vascular flow, vascular disease, biliary drainage, and histologic disease [63].

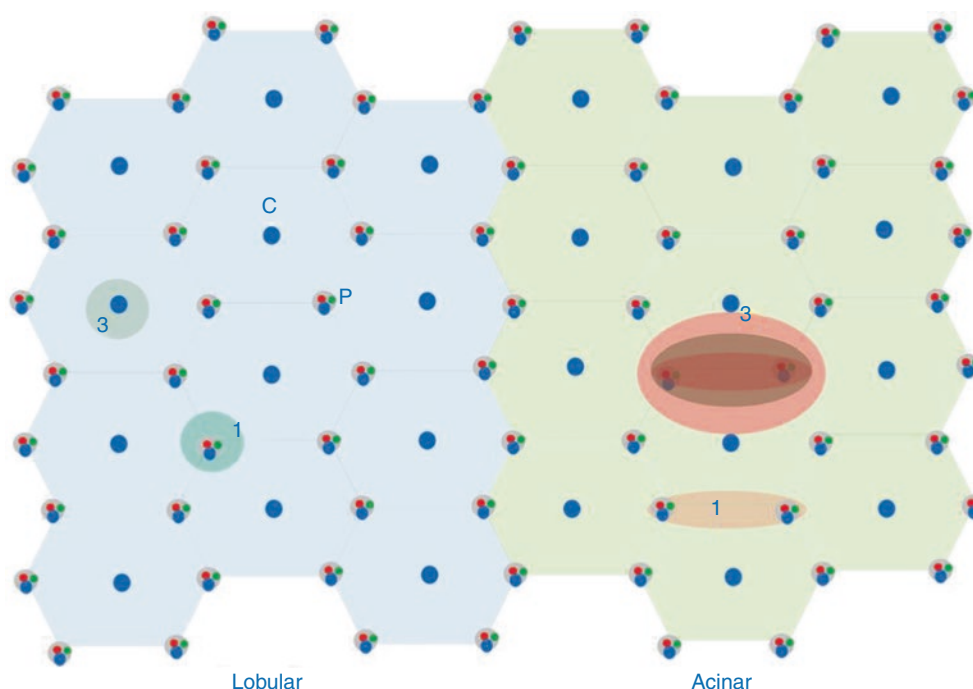
## 1.5 Liver Tests

### 1.5.1 Liver Biochemical Tests

Liver biochemical tests, traditionally called liver function tests, are a group of serum tests related to liver tissue injury or function. These biochemical tests represent liver at a static point in time and do not evaluate the true function of the liver. However, the term ‘liver function test’ has been used for many decades to represent the following assays: aspartate transferase (AST), alanine transferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase ( $\gamma$ -GT), lactic dehydrogenase (LDH), and bilirubin (total and direct). These tests relate to different aspects of liver tissue and are commonly used in evaluation of liver disease [64–68].

Aminotransferases (previously referred to as transaminases) are enzymes involved in the transfer of amino acid groups to keto groups. They are involved in gluconeogenesis. AST is involved in the transfer of aspartate amino acid to oxaloacetic acid, whereas ALT transfers alanine to pyruvic

**Fig. 1.5** Functional architecture of liver. On left liver architecture as per lobular distribution with zone 1 and zone 3 depicted. On the right pan-acinar architecture is depicted with its zone distribution (1–3) in relation to central vein and portal triads (Adapted from Suchy F. Hepatobiliary Function. In: Boron W, Boulpaep E, editors. Medical Physiology. 3rd ed. Philadelphia: Elsevier; 2017 and [55])



acid. Since these enzymes are present in hepatocytes, hepatocellular injury or disease results in elevation of these tests.

**Aspartate transferase AST** (previously called serum glutamic oxalo-acetic transaminase, or SGOT) is present in cytoplasm and mitochondria in most tissues, but in the liver, AST is predominantly present in the mitochondria of periportal hepatocytes (80%). Hence, an elevation in AST reflects mitochondrial injury of hepatocytes. The serum half-life of AST is 17 h [67], with a rapid decline occurring after an acute injury, such as ischemia or drug exposure. AST can be falsely elevated in patients with macro-AST, where it is bound to immunoglobulins and not eliminated [69]. AST can be falsely low in patients on chronic hemodialysis, with an associated pyridoxine deficiency.

**Alanine transferase ALT** (previously called serum glutamic pyruvic transaminase or SGPT) is present in the cytosol of liver tissue. An elevation of ALT is more suggestive of hepatocellular injury because it is less present in other organs, compared to AST. The serum half-life of ALT is 47 h [67].

**Alkaline phosphatase ALP** is bound to canalicular membranes of hepatocytes and associated with cholestatic diseases. This enzyme catalyzes the hydrolysis of phosphate esters. Magnesium and zinc are important cofactors, and their deficiency can result in relative reduction of ALP levels. ALP is also present in other tissues, such as placenta, bone, small bowel, kidney. More than 80% of ALP is derived from the liver and bone tissue, which can be differentiated by analysis of ALP isoenzymes. Elevated ALP is due to increased synthesis and secretion through canaliculi into sinusoids, with a half-life of 3 days [65, 70].

### 1.5.2 Synthetic Function Tests

**Bilirubin** is a breakdown product of hemoglobin. In the liver, unconjugated bilirubin (which is insoluble in water) is conjugated with glucuronic acid by UDP-glucuronyl transferase. Conjugated bilirubin (which is soluble in water) is secreted through bile. When the production of bilirubin exceeds the capacity of conjugation, such as in hemolysis, an elevation of serum unconjugated bilirubin is seen. There is also an increase in serum unconjugated bilirubin secondary to reduction of hepatic uptake or conjugation. This can be highlighted in conditions such as Gilbert's syndrome, where there is defect in UDP-glucuronyl transferase and subsequent unconjugated hyperbilirubinemia [48, 71].

Normally, serum bilirubin levels are low. However, in viral hepatitis, drug-induced liver injury or other acute processes, serum bilirubin may be elevated with concomitant increase in other liver tests, such as aminotransferases. Bilirubin may also be elevated in cholestatic or obstructive liver diseases with an associated increase in ALP. Bilirubin is also conjugated with albumin (8 bilirubin). Due to the longer half-life of albumin, reduction in bilirubin levels following clinical improvement takes a slower course [72].

**Albumin** synthesis is one of the important functions of the liver. Every day, 12–15 g of albumin are synthesized to maintain homeostasis. In patients with cirrhosis, there is a reduction in albumin synthesis, and serum albumin levels can correlate with severity of liver disease [36]. Thus, albumin levels are used in the Child Pugh scoring system and have

prognostic value. Serum albumin levels can be affected by other factors, including nutritional status, catabolism, urinary or gastrointestinal losses, and hormonal factors.

**Prothrombin time** measurement involves coagulation factors II, V, VII, and X. All of these factors are synthesized by the liver and can be affected by vitamin K. Prolongation of prothrombin time can reflect the reduction of liver synthetic function, vitamin K deficiency, or use of anticoagulants, such as warfarin. INR is a standardized measure of prothrombin time and can be used to assess disease severity and for prognostication [42–44].

### 1.5.3 Other Liver Tests

**Gamma glutamyl transferase ( $\gamma$ -GT)** is a membrane-bound enzyme that catalyzes transfer of  $\gamma$  glutamyl groups, such as glutathione, to other amino acids.  $\gamma$ -GT is found mostly around the epithelium lining of biliary ducts. Elevation of  $\gamma$ -GT is seen in cholestatic disease and typically associated with an elevation of ALP. Elevated  $\gamma$ -GT can confirm the biliary origin of ALP. However, certain cholestatic diseases (progressive familial intrahepatic cholestasis type I and type II and benign recurrent intrahepatic cholestasis type I) do not have an elevation of  $\gamma$ -GT.  $\gamma$ -GT may also be increased due to enzyme induction following alcohol consumption and the intake of certain medications [73].

**Lactic dehydrogenase (LDH)** is a cytoplasmic enzyme with five isoenzymes. They are non-specifically elevated in patients with ischemic hepatitis and neoplasm with hepatic involvement.

**5' Nucleotidase (5'NTD)** is a glycoprotein present in the cytoplasmic membrane and catalyzes the release of inorganic phosphate from nucleoside-5-phosphates. 5'NTD is present in many tissues and can be elevated in the setting of obstructive jaundice, parenchymal liver disease, hepatic metastases, and bone disease. 5'NTD correlates with ALP. When ALP and 5'NTD are concurrently elevated, the origin of ALP elevation is more likely related to the liver. This relationship is similar to that of  $\gamma$ GT and ALP [74].

**Ammonia** enters the circulation following gut metabolism of protein by intestinal bacteria and is incorporated into the urea cycle. In patients with liver disease, there is a decreased conversion of ammonia through the urea cycle and increased serum levels of ammonia can be present. Cerebral edema has been associated with ammonia levels  $>200$   $\mu\text{g/dl}$  in patients with acute liver failure [75]. Ammonia can also be raised in chronic liver disease with cirrhosis. However, the clinical utility of this test is limited. A single venous ammonia level is a static representation of liver function and does not correspond to the stage of encephalopathy.

**Bile acids** undergo intestinal reabsorption and enter the liver through portal circulation. The liver extracts the majority of bile acids on the first pass. Bile acids that are not extracted escape into the serum and can be analyzed. Although this estimation is not sensitive, serum bile acid elevation correlates with hepatobiliary disease [25].

### 1.5.4 Liver Tests: Pattern and Causes

The individual biochemical tests (mentioned above) are not specific for liver disease. Therefore, pattern recognition and clinical information are essential in diagnosing liver diseases. Abnormal liver tests are usually grouped into the following patterns: hepatocellular (predominant ALT and AST elevations), cholestatic (predominant ALP elevation), and mixed or infiltrative pattern. Bilirubin elevation can occur in any of these patterns, but isolated bilirubin elevation not usually seen.

A hepatocellular pattern (aminotransferase elevation) of liver injury is seen in alcoholic liver disease, nonalcoholic liver disease, autoimmune hepatitis, drug-induced liver injury, and viral hepatitis. In chronic liver disease, a mild to moderate ( $<5$  to 10 times the upper limit of normal) elevation of aminotransferase is seen. In acute liver injuries—such as drug injury (acetaminophen), ischemic liver disease, and acute hepatitis—a rapid elevation of aminotransferase to levels greater than 20 times the upper limit of normal can be found. Along with aminotransferase elevation, a simultaneous or subsequent elevation in bilirubin can also occur. There can be a varying degree of AST and ALT elevation in hepatocellular diseases, due to the pattern of injury and the source of AST and ALT. In alcoholic liver disease, there is a higher elevation in AST than ALT; whereas, in nonalcoholic liver disease, ALT is higher in pre-cirrhotic stages [64, 67, 68].

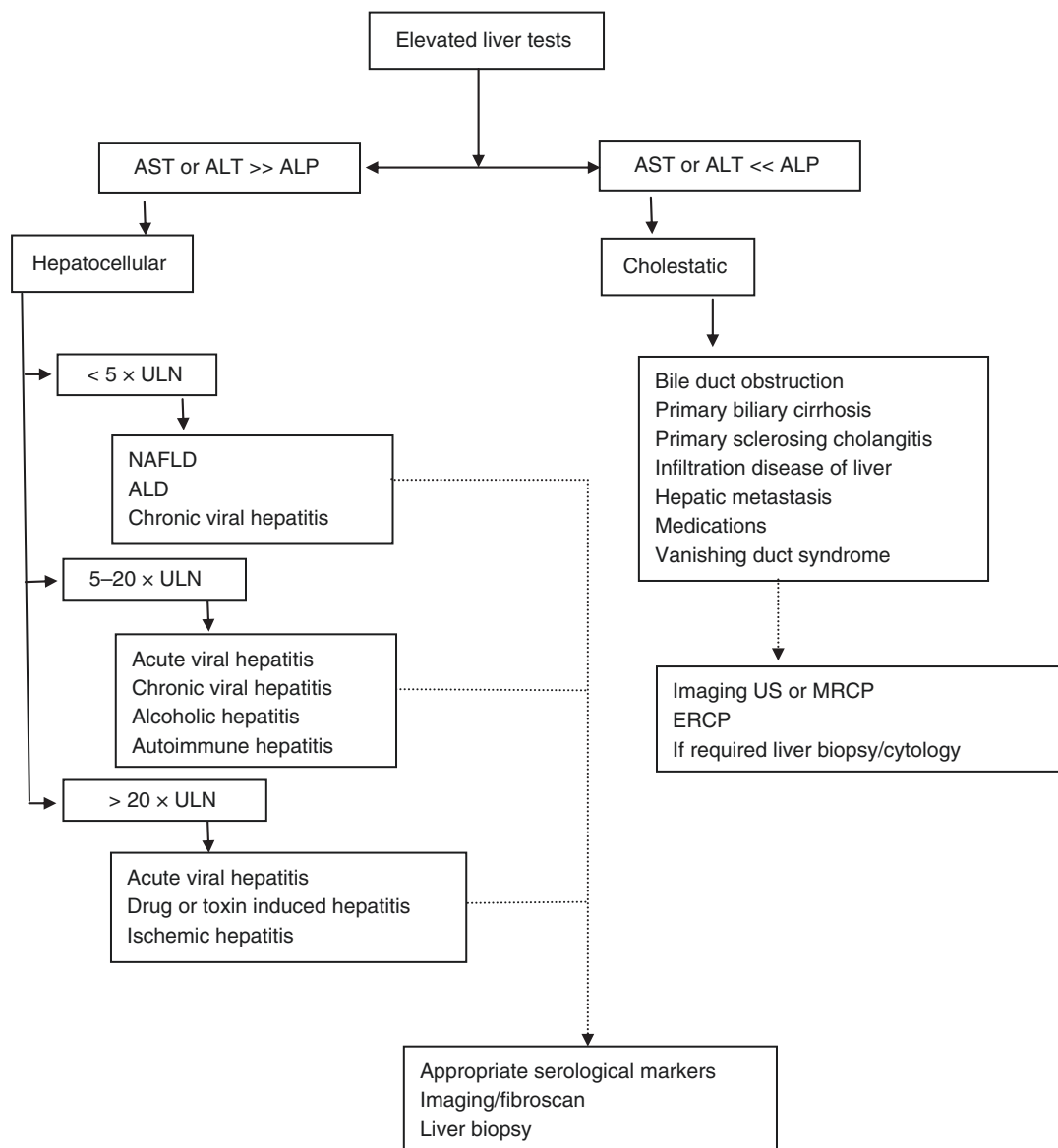
A cholestatic pattern (ALP elevation) of liver disease is seen with primary biliary cirrhosis, primary sclerosing cholangitis, intra- and extrahepatic cholestatic diseases (cholelithiasis, cholangiocarcinoma), infiltrative disorders (lymphoma, amyloidosis), and heart failure. Concurrent elevation of  $\gamma$ GT and/or 5' nucleotidase suggests a hepatic source of ALP. In many cases, there can be hyperbilirubinemia and a minimal elevation of ALT and AST. In contrast, low levels of ALP are seen in Wilson's disease with hemolysis, congenital hypophosphatasia, pernicious anemia, zinc deficiency, and severe hepatic insufficiency [64, 67, 76] (Table 1.2 and Fig. 1.6).

When a single biochemical liver test is elevated without other collaborative clinical features, alternative sources of this lab abnormality should be evaluated. Possible explanations include: hemolysis, for bilirubin elevation; skeletal or cardiac muscle injury, for AST elevation; and placenta, kidney, or bone sources, for ALP elevation.

**Table 1.2** Serum liver tests in evaluation of hepatic function and pathology

Function	Marker	Site of enzyme in liver/synthesis	Function	Non-liver sources of enzyme	Liver diseases with abnormality
<b>Hepatocellular</b>					
	Aspartate aminotransferase	Mitochondrial enzyme in hepatocytes zone 3 > zone 1	Catalyze transfer of amino group of aspartate amino acids permitting them to enter the citric acid cycle	Heart skeletal muscle, kidney, brain, red blood cell	$\leq 5$ ULN fatty liver, chronic viral hepatitis $5-20 \times$ ULN acute viral hepatitis, chronic viral hepatitis, alcoholic hepatitis, autoimmune hepatitis $> 20$ ULN Acute viral hepatitis, drug or toxin induced hepatitis, ischemic hepatitis
	Alanine aminotransferase	Cytosolic enzyme in hepatocytes zone 1 > zone 3	Catalyze transfer of amino group of alanine amino acids permitting them to enter the citric acid cycle	muscles, adipose tissues, intestines, colon, prostate, and brain	
<b>Cholestasis</b>					
	Alkaline phosphatase	Canalicular membrane of hepatocytes	Zinc metalloenzymes that catalyze the hydrolysis of organic phosphate esters	Bone, kidney intestine, leukocytes, placenta	Bile duct obstruction due to gallstones or tumor, sclerosing cholangitis, or bile duct stricture, infiltrative disease (such as sarcoidosis, hepatic abscesses, tuberculosis, and metastatic carcinoma)
	$\gamma$ -Glutamyl-transpeptidase	Microsomes of hepatocytes and biliary epithelial cells	Catalyzes transfer of $\gamma$ -glutamyl group from peptides to other amino acids.	Kidney, pancreas, intestine, spleen, heart, brain, and seminal vesicles	Correlate with liver origin of alkaline phosphatase in their elevation increase is also seen with enzyme induction with chronic alcohol use and medications (eg., rifampicin and phenytoin)
	5'-Nucleotidase	Canalicular and sinusoidal plasma membranes	Catalyzes the hydrolysis of nucleotides	Intestines, brain, heart, blood vessels, and endocrine pancreas	Correlate with liver origin of alkaline phosphatase in their elevation
	Bilirubin	<u>Synthesis</u> reticuloendothelial cells of spleen and liver <u>Transport</u> after conjugation	Breakdown product of hemolysis taken up by liver cells and conjugated to water soluble product excreted in bile		When associated with <u>ALP elevations</u> Indicate hepatic or extra-hepatic disorder <u>Other chronic liver diseases</u> Indicate reduced function of liver <u>Isolated elevation</u> Part of transport and conjugation defects or hemolysis
<b>Liver function mass</b>					
	Serum albumin	mRNA poly-ribosomes within the liver	Liver synthesizes albumin	Diet, increased loss from gut and kidney	When associated with liver disease—reduced function of liver
	Pro-thrombin time		Nearly all pro and anti-coagulant factors are synthesized in the liver		When associated with liver disease—reduced function of liver Use of anti-coagulations

ULN upper limit of normal; ALP alkaline phosphatase



**Fig. 1.6** Pattern of liver tests abnormalities and liver diseases. *ULN* upper limit of normal, *AST* aspartate amino transferase, *ALT* alanine amino transferase, *ALP* alkaline phosphatase, *NAFLD* non-alcoholic

fatty liver disease, *ALD* alcoholic liver disease, *US* ultrasound, *MRCP* magnetic resonance cholangio pancreatography, *ERCP* endoscopic retrograde cholangio pancreatography

## 1.5.5 Evaluation of Functional Capacity of Liver

### 1.5.5.1 Clinical and Biochemistry Based Scores

Liver tests provide information about the functional capacity of the liver. The combination of biochemical tests and clinical presentation can yield a better assessment of liver function, disease prognosis, and disease outcome. The most commonly used tools that incorporate both biochemical and clinical information are the Child Pugh score and Model for End stage Liver Disease (MELD) score.

The Child Pugh score is weighted for clinical severity, with ascites and encephalopathy, and it also includes bio-

chemical measurements of serum albumin, bilirubin and prothrombin time. This score is a useful tool to prognosticate long-term survival in patients with cirrhosis. The tool is helpful in guiding care for cirrhotic patients in many clinical settings, such as following surgery.

The MELD score is a combination of serum bilirubin, creatinine, and INR. Originally, it was devised to evaluate risk for patients following a transvenous intrahepatic portosystemic shunt (TIPS) procedure. The MELD score has since been shown to predict the 90-day mortality in patients with cirrhosis and is currently used to evaluate and prioritize patients for liver transplantation [77]. With its inverse relationship to liver function, the MELD score



has been found to successfully predict outcomes in various situations among patients with end-stage liver disease.

#### 1.5.5.2 Dynamic Liver Function Tests

Static liver tests are obtained to evaluate liver abnormalities. Dynamic liver tests are performed over a specific period of time to assess liver function abnormalities. These dynamic studies usually involve infusion or ingestion of an active agent, followed by a quantitative assessment of hepatic metabolism and/or clearance of these agents over a period of time. Dynamic studies estimate the functional capacity of the liver at the time of evaluation. These studies include the rose bengal, indocyanine green, bromosulphthalein, caffeine, amino acid clearance, galactose elimination capacity, monoethylglycincxyllidide and aminopyrine tests.

##### Rose Bengal Test

After infusion of  $I^{131}$  Rose Bengal dye, liver extraction of this dye is assessed at minute 4 and 8. A decreased uptake by the liver is suggestive of increased presence in the serum, signifying liver dysfunction. The rose Bengal test was one of the earliest assays of liver function but has since been replaced by newer assays [78].

##### Indocyanine Green Clearance Test

Indocyanine green is almost exclusively eliminated by the liver and appears in bile acids within 8 min of intravenous infusion. Indocyanine green does not undergo intrahepatic re-circulation. Following intravenous injection of indocyanine green, clearance rate and plasma disappearance rate can be assessed noninvasively by a transcutaneous system. In normal individuals, the clearance rate of indocyanine green is greater than 700 ml/min/m<sup>2</sup> and its plasma disappearance rate is greater than 18%/min. A decrease in indocyanine green plasma disappearance rate can be seen in patients with liver dysfunction or septic shock. This study can prognosticate patients undergoing liver resection and is used in evaluating the liver function of potential donors [79].

##### Bromosulphthalein Clearance Test

Following its intravenous injection, bromosulphthalein is extracted rapidly and exclusively by the liver. In normal individuals, <10% remains in the serum by 30 min and <5% by 45 min. Extraction and removal of bromosulphthalein by the liver is related to hepatic blood flow and canalicular bile transporter protein function. Slower rates of extraction are seen in liver disease. Increased retention rates at 15 min have a negative prognosis for patients undergoing liver resection. Also, the bromosulphthalein clearance test can differentiate Dubin-Johnson syndrome from Rota syndrome [79].

##### Aminopyrine Test

Following an oral ingestion of radioactively labeled aminopyrine, periodic quantification of  $^{14}CO_2$  in exhaled air can evaluate liver function. This test evaluates the microsomal function of the liver (demethylation). This study is limited because it can be influenced by factors other than liver function, such as gastrointestinal motility and basal metabolic rate [79].

##### Caffeine Test

The caffeine test is considered a quantitative test of hepatic microsomal activity. It correlates well with the bromosulphthalein clearance test and the  $^{14}CO_2$  breath elimination test. The caffeine test also has the advantage of oral administration. Following oral ingestion of a defined amount (300 mg) of caffeine, caffeine and caffeine metabolite levels are periodically quantified in the blood. Patients with cirrhosis have been found to have longer caffeine elimination rates and lower caffeine metabolite to caffeine ratios [79].

##### Miscellaneous Tests

Other tests use a similar principle of serum clearance to assess liver function. These include the amino acid clearance test, which looks at periodic plasma clearance of amino acids after a standardized infusion dose. Galactose elimination capacity assesses the clearance of galactose, but also assesses the liver's capacity to convert galactose to its phosphorylated form: galactose-1-phosphate. This latter study is not affected by insulin secretion and can also be a measure of hepatic blood flow. These studies are rarely performed in clinical practice.

In summary, the liver plays a vital role in many metabolic processes such as absorption of nutrients and metabolically active agents from the gut, while maintaining its own immunity. In order to effectively perform its many roles, the liver has a complex architectural pattern of vascular supply and drainage. The liver undergoes continued exposure to metabolic agents, which have the potential to be detrimental to hepatic function. Due to this complexity, it is difficult to properly assess liver function with a single or small group of tests.

## 1.6 Questions

1. A 36-year-old woman presents to the hospital with worsening abdominal pain despite taking 30 acetaminophen (500 mg each) tablets in a day. Other than abdominal discomfort at examination was normal. Her labs show AST 3278 IU, ALT 2968 IU, bilirubin 2.0 mg/dl, INR 5.2, creatinine 0.8 mg/dl. Her AST and ALT improved initially in the first few days following presentation but plateaued after with evaluation of bilirubin. A liver biopsy was performed to look for causes of persistent elevation of AST

and ALT. Liver biopsy features which will concur with acetaminophen induced drug injury are

- a) zone 3 necrosis with collapse of lobules
  - b) diffuse infiltration with plasma cell
  - c) severe fatty changes of liver
  - d) cirrhosis
2. She continues to improve following this and her aminotransferases normalizes (AST 11 and ALT 18 IU) in 3 weeks. On her 12 month-follow-up by her family practice physician her AST is elevated to 84 IU and ALT 40 IU. Her physician should be concerned about
    - a) diabetes or hypertriglyceridemia causing fatty liver disease
    - b) familial liver disease which contributed to acute liver injury earlier
    - c) excessive alcohol intake
    - d) another acetaminophen poisoning
  3. She is lost to follow-up following this for 10 years and is seen in the emergency room with jaundice abdominal distention and pedal edema. Her liver ultrasound shows fatty liver with ascites. An astute medical student who initially examines her calculates MELD score and Child Pugh score as 22 and 10. Her AST on this visit is 312, ALT 121 IU, ALP 124, bilirubin 5.6 mg/dl, INR 2.1, creatinine 0.6 mg/dl. Which of the following is valid in relation to her clinical features?
    - a) has high risk of 90 day mortality
    - b) her continued use of alcohol contributes to the current liver disease
    - c) has chronic liver disease with decompensation
    - d) all of the above
    - e) none of the above
  4. She was managed for acute alcoholic hepatitis and discharged during this hospitalization and was instructed to quit alcohol. She's being followed by her family practice physician periodically and a year later her repeat labs are AST 42, ALT 39 IU, ALP 124, bilirubin 1.6 mg/dl, INR 1.1, creatinine 0.6 mg/dl. She currently does not have ascites or confusion requiring treatment. Compared to an earlier state she has
    - a) better survival
    - b) poorer survival
    - c) lower MELD in Child Pugh score
    - d) higher MELD in Child Pugh score
    - e) A and C
    - f) B and D

### 1.6.1 Answers

1. a, 2. c, 3. d, 4. e

## References

1. Mathuram P, Chirachariyavej T, Peonim AV, Rochanawutanon M. Correlation of internal organ weight with body weight and length in normal Thai adults. *J Med Assoc Thai*. 2009;92(2):250–8.
2. Garby L, Lammert O, Kock KF, Thobo-Carlson B. Weights of brain, heart, liver, kidneys, and spleen in healthy and apparently healthy adult danish subjects. *Am J Hum Biol*. 1993;5(3):291–6.
3. Wanless IR. Physioanatomic considerations. In: Schiff's diseases of the liver. Hoboken, NJ: Wiley-Blackwell; 2011. p. 87–119.
4. Suchy F. Hepatobiliary function. In: Boron W, Boulpaep E, editors. *Medical physiology*. 3rd ed. Philadelphia, PA: Elsevier; 2017. p. 944–71.
5. Goldsmith NA, Woodburne RT. The surgical anatomy pertaining to liver resection. *Surg Gynecol Obstet*. 1957;105(3):310–8.
6. Bismuth H. Revisiting liver anatomy and terminology of hepatectomies. *Ann Surg*. 2013;257(3):383–6.
7. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. *World J Gastroenterol*. 2010;16(48):6046–57.
8. Bioulac-Sage P, Saric J, Balabaud C. Microscopic anatomy of the intrahepatic circulatory system. In: Okuda K, Benhamou J, editors. *Portal hypertension: clinical and physiological aspects*. Tokyo: Springer Japan; 1991. p. 13–26.
9. Douglass BE, Baggenstoss AH, Hollinshead WH. The anatomy of the portal vein and its tributaries. *Surg Gynecol Obstet*. 1950;91(5):562–76.
10. Michels NA. Newer anatomy of the liver and its variant blood supply and collateral circulation. *Am J Surg*. 1966;112(3):337–47.
11. Lunderquist A. Arterial segmental supply of the liver. An angiographic study. *Acta Radiol Diagn (Stockh)*. 1967;Suppl 272:1+.
12. Daseler EH, Anson BJ. The cystic artery and constituents of the hepatic pedicle; a study of 500 specimens. *Surg Gynecol Obstet*. 1947;85(1):47–63.
13. Honda H, Yanaga K, Onitsuka H, Kaneko K, Murakami J, Masuda K. Ultrasonographic anatomy of veins draining the left lobe of the liver. feasibility of live related transplantation. *Acta Radiol*. 1991;32(6):479–84.
14. Tavill AS, Wood EJ, Kreel L, Jones EA, Gregory M, Sherlock S. The Budd-Chiari syndrome: correlation between hepatic scintigraphy and the clinical, radiological, and pathological findings in nineteen cases of hepatic venous outflow obstruction. *Gastroenterology*. 1975;68(3):509–18.
15. Okuda K, Matsutani S. Portal-systemic collaterals: anatomy and clinical implications. In: Okuda K, Benhamou J, editors. *Portal hypertension: clinical and physiological aspects*. Tokyo: Springer Japan; 1991. p. 51–62.
16. Philips CA, Arora A, Shetty R, Kasana V. A comprehensive review of portosystemic collaterals in cirrhosis: historical aspects, anatomy, and classifications. *Int J Hepatol*. 2016;2016:6170243.
17. Popper H, Elias H, Petty DE. Vascular pattern of the cirrhotic liver. *Am J Clin Pathol*. 1952;22(8):717–29.
18. Trutmann M, Sasse D. The lymphatics of the liver. *Anat Embryol (Berl)*. 1994;190(3):201–9.
19. Timmermans JP, Geerts A. Nerves in liver: superfluous structures? A special issue of the anatomical record updating our views on hepatic innervation. *Anat Rec B New Anat*. 2005;282(1):4.
20. Nakanuma Y, Hosoi M, Sanzen T, Sasaki M. Microstructure and development of the normal and pathologic biliary tract in humans, including blood supply. *Microsc Res Tech*. 1997;38(6):552–70.
21. Dowdy GS Jr, Waldron GW, Brown WG. Surgical anatomy of the pancreatobiliary ductal system. observations. *Arch Surg*. 1962;84:229–46.
22. Boyden EA. The anatomy of the choledochoduodenal junction in man. *Surg Gynecol Obstet*. 1957;104(6):641–52.

23. Corless JK, Middleton HM III. Normal liver function. A basis for understanding hepatic disease. *Arch Intern Med.* 1983;143(12):2291–4.
24. Russell DW. Cholesterol biosynthesis and metabolism. *Cardiovasc Drugs Ther.* 1992;6(2):103–10.
25. Mukherjee S, Gollan JL. Assessment of liver function. In: *Sherlock's diseases of the liver and biliary system.* Chichester: Wiley-Blackwell; 2011. p. 20–35.
26. Mansbach CM II, Gorelick F. Development and physiological regulation of intestinal lipid absorption. II. Dietary lipid absorption, complex lipid synthesis, and the intracellular packaging and secretion of chylomicrons. *Am J Physiol Gastrointest Liver Physiol.* 2007;293(4):G645–50.
27. Solaymani-Dodaran M, Aithal GP, Card T, West J. Risk of cardiovascular and cerebrovascular events in primary biliary cirrhosis: a population-based cohort study. *Am J Gastroenterol.* 2008;103(11):2784–8.
28. Sacks FM. The apolipoprotein story. *Atheroscler Suppl.* 2006;7(4):23–7.
29. Lefkowitz JH. Anatomy and function. In: *Sherlock's diseases of the liver and biliary system.* Chichester: Wiley-Blackwell; 2011. p. 1–19.
30. Rui L. Energy metabolism in the liver. *Compr Physiol.* 2014;4(1):177–97.
31. Moseley RH. Hepatic amino acid transport. *Semin Liver Dis.* 1996;16(2):137–45.
32. Morgan MY, Marshall AW, Milsom JP, Sherlock S. Plasma amino-acid patterns in liver disease. *Gut.* 1982;23(5):362–70.
33. Tavill AS. The synthesis and degradation of liver-produced proteins. *Gut.* 1972;13(3):225–41.
34. Herlong HF, Mitchell MC. Laboratory tests. In: *Schiff's diseases of the liver.* Hoboken, NJ: Wiley-Blackwell; 2011. p. 17–43.
35. Tavill AS, Craigie A, Rosenoer WM. The measurement of the synthetic rate of albumin in man. *Clin Sci.* 1968;34(1):1–28.
36. Barle H, Nyberg B, Essen P, Andersson K, McNurlan MA, Wernerman J, Garlick PJ. The synthesis rates of total liver protein and plasma albumin determined simultaneously in vivo in humans. *Hepatology.* 1997;25(1):154–8.
37. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. *Hepatology.* 1988;8(2):385–401.
38. Rothschild MA, Oratz M, Zimmon D, Schreiber SS, Weiner I, Van Caneghem A. Albumin synthesis in cirrhotic subjects with ascites studied with carbonate-14C. *J Clin Invest.* 1969;48(2):344–50.
39. Terada K, Kawarada Y, Miura N, Yasui O, Koyama K, Sugiyama T. Copper incorporation into ceruloplasmin in rat livers. *Biochim Biophys Acta.* 1995;1270(1):58–62.
40. Pietrangelo A. Physiology of iron transport and the hemochromatosis gene. *Am J Physiol Gastrointest Liver Physiol.* 2002;282(3):G403–14.
41. Dinarello CA. Interleukin-1 and the pathogenesis of the acute-phase response. *N Engl J Med.* 1984;311(22):1413–8.
42. Olson JP, Miller LL, Troup SB. Synthesis of clotting factors by the isolated perfused rat liver. *J Clin Invest.* 1966;45(5):690–701.
43. Mattii R, Ambrus JL, Sokal JE, Mink I. Production of members of the blood coagulation and fibrinolysin systems by the isolated perfused liver. *Proc Soc Exp Biol Med.* 1964;116:69–72.
44. Rapaport SI, Ames SB, Mikkelsen S, Goodman JR. Plasma clotting factors in chronic hepatocellular disease. *N Engl J Med.* 1960;263:278–82.
45. Ellison RT III, Horsburgh CR Jr, Curd J. Complement levels in patients with hepatic dysfunction. *Dig Dis Sci.* 1990;35(2):231–5.
46. Fukuda Y, Nagura H, Asai J, Satake T. Possible mechanisms of elevation of serum secretory immunoglobulin A in liver diseases. *Am J Gastroenterol.* 1986;81(5):315–24.
47. Hofmann AF. Bile acids: Trying to understand their chemistry and biology with the hope of helping patients. *Hepatology.* 2009;49(5):1403–18.
48. Lester R, Schmid R. Bilirubin metabolism. *N Engl J Med.* 1964;270:779–86.
49. Pikuleva IA. Cytochrome P450s and cholesterol homeostasis. *Pharmacol Ther.* 2006;112(3):761–73.
50. Wolkoff AW, Cohen DE. Bile acid regulation of hepatic physiology: I. Hepatocyte transport of bile acids. *Am J Physiol Gastrointest Liver Physiol.* 2003;284(2):G175–9.
51. Raymond GD, Galambos JT. Hepatic storage and excretion of bilirubin in man. *Am J Gastroenterol.* 1971;55(2):135–44.
52. Carulli N, Bertolotti M, Carubbi F, Concarì M, Martella P, Carulli L, Loria P. Review article: effect of bile salt pool composition on hepatic and biliary functions. *Aliment Pharmacol Ther.* 2000;14(Suppl 2):14–8.
53. Robb BW, Matthews JB. Bile salt diarrhea. *Curr Gastroenterol Rep.* 2005;7(5):379–83.
54. Racanelli V, Rehmann B. The liver as an immunological organ. *Hepatology.* 2006;43(2 Suppl 1):S54–62.
55. Bogdanos DP, Gao B, Gershwin ME. Liver immunology. *Compr Physiol.* 2013;3(2):567–98.
56. Cholongitas E, Senzolo M, Standish R, Marelli L, Quaglia A, Patch D, Dhillon AP, et al. A systematic review of the quality of liver biopsy specimens. *Am J Clin Pathol.* 2006;125(5):710–21.
57. West AB. The liver. An atlas and text of ultrastructural pathology. By M. J. Phillips, S. Poucell, J. Patterson and P. Valencia, 585 pp. New York: Raven Press, 1987. \$95.00. *Hepatology.* 1989;9(4):659.
58. Wisse E, Braet F, Luo D, De Zanger R, Jans D, Crabbe E, Vermoesen A. Structure and function of sinusoidal lining cells in the liver. *Toxicol Pathol.* 1996;24(1):100–11.
59. Roskams TA, Theise ND, Balabaud C, Bhagat G, Bhathal PS, Bioulac-Sage P, Brunt EM, et al. Nomenclature of the finer branches of the biliary tree: canals, ductules, and ductular reactions in human livers. *Hepatology.* 2004;39(6):1739–45.
60. Mathew J, Geerts A, Burt AD. Pathobiology of hepatic stellate cells. *Hepato-Gastroenterology.* 1996;43(7):72–91.
61. Bioulac-Sage P, Kuiper J, Van Berkel TJ, Balabaud C. Lymphocyte and macrophage populations in the liver. *Hepato-Gastroenterology.* 1996;43(7):4–14.
62. Rappaport AM. Hepatic blood flow: morphologic aspects and physiologic regulation. *Int Rev Physiol.* 1980;21:1–63.
63. Lamers WH, Hilberts A, Furt E, Smith J, Jonges GN, van Noorden CJ, Janzen JW, et al. Hepatic enzymic zonation: a reevaluation of the concept of the liver acinus. *Hepatology.* 1989;10(1):72–6.
64. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology.* 2002;123(4):1367–84.
65. Gowda S, Desai PB, Hull VV, Math AA, Vernekar SN, Kulkarni SS. A review on laboratory liver function tests. *Pan Afr Med J.* 2009;3:17.
66. Rochling FA. Evaluation of abnormal liver tests. *Clin Cornerstone.* 2001;3(6):1–12.
67. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ.* 2005;172(3):367–79.
68. Kasarala G, Tillmann HL. Standard liver tests. *Clin Liver Dis.* 2016;8(1):13–8.
69. Caropreso M, Fortunato G, Lenta S, Palmieri D, Esposito M, Vitale DF, Iorio R, et al. Prevalence and long-term course of macro-aspartate aminotransferase in children. *J Pediatr.* 2009;154(5):744–8.
70. Weiss MJ, Ray K, Henthorn PS, Lamb B, Kadesch T, Harris H. Structure of the human liver/bone/kidney alkaline phosphatase gene. *J Biol Chem.* 1988;263(24):12002–10.
71. Elias E. Jaundice and cholestasis. In: *Sherlock's diseases of the liver and biliary system.* Chichester: Wiley-Blackwell; 2011. p. 234–56.



72. Fevery J, Blanckaert N. What can we learn from analysis of serum bilirubin? *J Hepatol.* 1986;2(1):113–21.
73. Rollason JG, Pincherle G, Robinson D. Serum gamma glutamyl transpeptidase in relation to alcohol consumption. *Clin Chim Acta.* 1972;39(1):75–80.
74. Eschar J, Rudzki C, Zimmerman HJ. Serum levels of 5'-nucleotidase in disease. *Am J Clin Pathol.* 1967;47(5):598–606.
75. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology.* 1999;29(3):648–53.
76. Agrawal S, Dhiman RK, Limdi JK. Evaluation of abnormal liver function tests. *Postgrad Med J.* 2016;92(1086):223–34.
77. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001;33(2):464–70.
78. Lowenstein JM. Radioactive rose bengal test as a quantitative measure of liver function. *Proc Soc Exp Biol Med.* 1956;93(2):377–8.
79. Sakka SG. Assessing liver function. *Curr Opin Crit Care.* 2007;13(2):207–14.

---

## Further Reading

- Schiff's diseases of the liver. 11th ed. Wiley-Blackwell; 2011.
- Sherlock's diseases of the liver and biliary system. 12th ed. Wiley-Blackwell; 2011.
- Boyer TD, Manns MP, Sanyal AJ, editors. Zakim and Boyer's hepatology. 6th ed. Saint Louis, MI: W.B. Saunders; 2012.

Kathleen Heintz and Steven M. Hollenberg

## Abstract

The principle hemodynamic abnormality in patients with cirrhosis and portal hypertension is systemic vasodilation with a hyperdynamic circulatory syndrome in which cardiac output and heart rate are increased and systemic vascular resistance is decreased. This is mediated by both structural changes in the splanchnic circulation that decrease circulating blood volume and humoral changes with release of several vasoactive substances that decrease arterial tone in the systemic circulation. Despite this hyperdynamic circulatory state, the heart may not be normal; careful investigation has revealed a number of cardiovascular abnormalities, including diastolic dysfunction, blunted systolic response to stress, and electrophysiologic abnormalities, which together have been termed ‘cirrhotic cardiomyopathy.’

## Keywords

Cirrhotic cardiomyopathy • Portal hypertension • Splanchnic vasodilation • Nitric oxide • Carbon monoxide • cannabinoids

## 2.1 Introduction

The observation of hyperdynamic circulation in liver disease has been recognized for more than 50 years. In 1953, Kowalski and Abelman, described “warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nailbed,” in patients with alcoholic cirrhosis [1]. The pathophysiology of impaired liver function and liver cirrhosis is associated with significant hemodynamic and cardiovascular changes. The normal liver architecture is distorted in cirrhosis, producing changes in the splanchnic circulation, but there are also humoral changes that decrease arterial tone in the systemic circulation [2]. Due to systemic vasodilation, portal hypertension is associated with a hyperdynamic circulatory syndrome in which cardiac output and heart rate are increased and systemic vascular resistance is

decreased. Reduction of mesenteric arterial resistance is mediated by the release of several vasoactive substances, most notably nitric oxide (NO), but other molecules are involved. This decrease in effective circulatory volume triggers baroreceptor-mediated activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), resulting in sodium and water retention with eventual formation of ascites. Despite a hyperdynamic circulatory state, the heart may not be normal; careful investigation has revealed a number of cardiovascular abnormalities, including diastolic dysfunction, blunted systolic response to stress, and electrophysiologic abnormalities, which together have been termed ‘*cirrhotic cardiomyopathy*.’

Accumulating evidence suggests that cirrhosis-related cardiovascular abnormalities play a major role in the pathogenesis of multiple life-threatening complications including hepatorenal syndrome, ascites, spontaneous bacterial peritonitis, gastroesophageal varices, and hepatopulmonary syndrome [3]. This chapter outlines the progressive changes leading to cardiac dysfunction and a cirrhotic cardiomyopathy.

K. Heintz, D.O. • S.M. Hollenberg, M.D. (✉)  
Department of Cardiovascular Disease, Cooper University  
Hospital, Camden, NJ, USA  
e-mail: [Hollenberg-steven@cooperhealth.edu](mailto:Hollenberg-steven@cooperhealth.edu)

## 2.2 Initial Circulatory Changes

Portal hypertension is defined as pathological increase in portal vein pressure and is diagnosed when the hepatic venous pressure gradient is above the normal range (1–5 mmHg) [4]. Liver cirrhosis is the most frequent cause of portal hypertension in western countries. When the hepatic venous pressure gradient increases to 10 mm Hg or more, portal hypertension of cirrhosis eventually results in severe complications including ascites, hepatorenal syndrome, hepatic encephalopathy and potential hemorrhage from variceal bleeding [4]. Circulatory changes result from multiple pathophysiological mechanisms, including neurogenic, humoral, and vascular dysregulation [3]. Progressive vasodilation results in portal hypertension, multiorgan involvement and eventual hemodynamic collapse. Patients with chronic liver disease develop hyperdynamic circulation and maladaptive systemic changes well before end stage cirrhotic cardiomyopathy becomes clinically apparent.

## 2.3 Cirrhotic Cardiomyopathy vs. Cardiac Cirrhosis

Cirrhotic cardiomyopathy should not be confused with the similar sounding term, ‘cardiac cirrhosis,’ which describes a congestive hepatopathy secondary to right sided heart failure. This generally less serious condition is improved by effective treatment for right sided heart failure [5]. *Cardiac cirrhosis*, also termed congestive hepatopathy, is liver dysfunction consequent to right-sided heart failure. The recognition and diagnosis of congestive hepatopathy due to heart failure is important, as optimization of cardiac performance may lead to improvement in or even recovery of liver function. The key mechanism underlying cardiac cirrhosis is passive congestion secondary to increased right ventricular filling pressures [5]. Right heart failure leading to congestive hepatopathy is characterized by edema, ascites, and hepatomegaly. Laboratory values generally reveal cholestasis with an elevated alkaline phosphatase and bilirubin, while transaminases may only be mildly increased.

*Cirrhotic Cardiomyopathy* describes cardiovascular dysfunction in patients with advanced liver disease. Due to the high cardiac output in some patients with cirrhosis, it was often assumed that cardiac function was normal. Cardiac dysfunction was recognized in some patients, but for many years was attributed to alcoholic cardiomyopathy. Over the last 20 years, it has been shown that cardiac dysfunction exists in non-alcoholic cirrhotic patients without known cardiac disease and may even precede complications such as hepatorenal syndrome [6]. Despite hyperdynamic circulation at rest, studies have shown a blunted cardiac response to stress or exercise that suggest unmasking of latent cardiac dysfunction [7]. This syndrome, termed cirrhotic cardiomyopathy, is summarized in Table 2.1.

To fully understand the complexity of changes in circulatory physiology, a grasp of systemic, hepatic and splanchnic

**Table 2.1** Characteristics of cirrhotic cardiomyopathy

• Impaired left ventricular systolic function with stress
• Absence of other known cardiac disease prior to diagnosis of liver failure
• Left ventricular hypertrophy
• Left ventricular diastolic dysfunction
• Electrophysiologic abnormalities

circulation is essential. The healthy liver is a compliant organ with very low resistance. The celiac artery, along with the superior and inferior mesenteric arteries, provides blood to the major abdominal organs. The splanchnic circulation functions as a parallel circulatory reservoir between the systemic circulation of the abdominal organs, draining into the portal vein and the liver, before blood returns to the inferior vena cava, and finally to the heart. The splanchnic circulation regulates circulating blood volume and blood pressure by its ability to vasodilate and vasoconstrict in response to circulatory demands. For instance, in the case of acute hypovolemia, the splanchnic circulation becomes significantly reduced, allowing blood to be shunted to the heart and the brain. In the case of a large meal, the volume within splanchnic circulation, which is usually more than 1000 ml/min, can double to accommodate digestion. These changes are modulated by metabolic, vasoreactive, and chemical regulators. Many factors contribute to the chronic circulatory changes and eventual cardiovascular decline in liver disease.

## 2.4 Portal Hypertension: The Process

The splanchnic circulation, which also includes the portal vein, is responsible for transporting blood from the abdominal organs to the liver. The functional unit of the liver is the hepatic acinus [8, 9]. There are approximately 100,000 acini per human liver. The acinus represents a cluster of parenchymal cells approximately 2 mm in diameter, lined with Kupffer cells, which are specialized phagocytic macrophages that break down hemoglobin. Kupffer cells constitute approximately 80% of the total macrophages in the body. They participate in clearing toxins from the body. They are also capable of secreting mediators, such as cytokines, endothelins, and nitric oxide, in response to inflammation [10].

The acini are grouped around terminal branches of the hepatic arteriole and the portal venule [11]. The acini have been likened to clusters of berries suspended on a vascular stalk. The vascular stalk enters the center of acinus, the so called, ‘axle of the wheel.’ Blood from the hepatic artery and the portal vein enter the acini through this central blood supply, and flow out to the periphery, producing strong gradients of flow for oxygen and other substances exchanged. The flow in the acinus is divided into zones. The flow in Zone 1, nearest to the vascular stalk, is the strongest. Zone 1 parenchymal cells receive the richest supply of oxygen and nutrients. Zone 1 is also exposed

to higher levels of drugs and toxins. Zone 3 lies on the periphery, and is supplied by blood which has already flowed through Zone 1 and 2. Zone 3 is richest in microsomal enzymes [10]. In cirrhosis, as the liver becomes diseased, collagen is deposited in the hepatic acinus, narrowing the sinusoidal lumen. This limits the cross sectional area of the hepatic sinusoids, leading to slow flow, with an increase in hepatic resistance [2]. The initial vascular resistance to portal blood flow is dependent on two factors: the intrahepatic resistance and the resistance generated by the collateral circulation [4].

In late portal hypertension, features consistent with cirrhotic cardiomyopathy include an increase in heart rate and resting cardiac output, decreased arterial blood pressure and thus systemic vascular resistance, and reduced myocardial response to stress conditions, along with histological changes to cardiac chambers, electrophysiological abnormalities, and serum markers suggestive of cardiac stress. In the absence of known cardiac disease, these abnormalities are described as a *cirrhotic cardiomyopathy* [12].

### 2.4.1 Early Cirrhosis

Early in the process, portal hypertension is primarily due to increased *intrahepatic* vascular resistance [13]. Classically, structural distortion of the intrahepatic vasculature, as a consequence of fibrosis, scarring and vascular thrombosis, has been considered the only cause of the increased intrahepatic vascular resistance [4]. Additional studies demonstrated that a dynamic component, represented by contractile elements of the hepatic vascular bed, may contribute to the increased intrahepatic vascular tone [14].

Multiple hepatic vasoactive substances contribute to worsening portal hypertension. There is an increased production of vasoconstrictors, and a deficient release of vasodilators. This, in combination with an exaggerated response to vasoconstrictors, and an impaired vasodilatory response of the hepatic vascular bed, are responsible for the increased dynamic component of intrahepatic vascular resistance [15]. Endothelin (ET) appears to play a major role in the enhanced hepatic vascular tone [16].

### 2.4.2 Late Cirrhosis

Later, in moderate to severe portal hypertension, extensive collateral circulation develops, with significant portal-systemic shunting in splanchnic blood flow prior to entry into the portal vein [13]. The signal that initiates splanchnic dilatation is the increase in portal pressure, which triggers a molecular mechanism that initiates the vasodilatory stimulus [17]. Systemic vascular resistance may be reduced due to arteriovenous communications from splanchnic shunting, an increase in circulating vasodilators, reduced resistance to vasoconstrictors, and an increased sensitivity

to vasodilators. Vasodilators may avoid degradation due to a diseased liver, or escape through the portosystemic collateral circulation [12].

## 2.5 Circulation in Cirrhosis

Changes in the peripheral vascular resistance of the splanchnic vascular bed are compensated by an increase in cardiac output. The development of portal hypertension is gradual. There is a redistribution of volume toward the splanchnic circulation and away from the systemic circulation. Early portal hypertension is often unnoticed. It is the slow progression of disease that allows dysfunctional compensatory mechanisms to occur, also often unnoticed. This redistribution results in effective hypovolemia. Low effective blood volume, along with arterial hypotension, lead to volume and baroreceptor activation of the sympathetic nervous system and the renin angiotensin aldosterone system [12]. There is sodium and water retention, expansion of the plasma volume, with aggravation of an already hyperdynamic condition [13]. A schematic of the process is shown in Fig. 2.1.

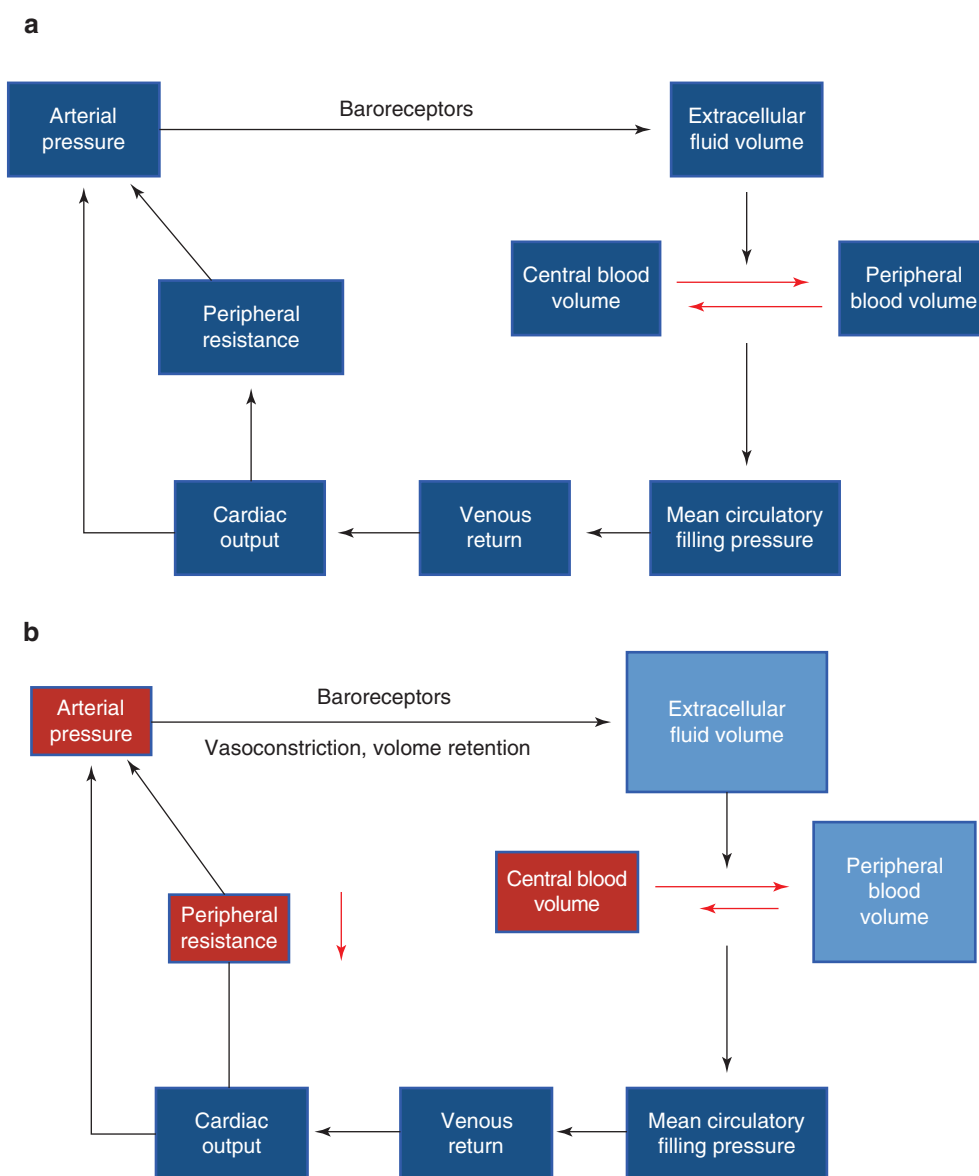
Impaired cardiovascular responsiveness in cirrhosis is likely due to a combination of factors that include cardiomyocyte plasma membrane alterations, attenuated stimulatory pathways, and enhanced activity of inhibitory systems [3]. There is a decreased ventricular response to stress. The cardiac response to exercise is blunted. On stress testing cirrhotic patients have impaired increase in ejection fraction, chronotropic incompetence, and decreased cardiac index [18]. This impaired cardiac performance occurs in alcoholic and nonalcoholic cirrhotic patients and may be dependent on the amount of hepatic failure [19]. Histological changes include a heart weight that is increased, dilatation of cardiac chambers with hypertrophy, and structural changes including myocardial cell edema and fibrosis [19]. These alterations may be due to circulating factors, which are discussed in detail below.

Specific criteria for cirrhotic cardiomyopathy do not exist, and so its true incidence is unknown. The characteristics of cirrhotic cardiomyopathy are listed in Table 2.1.

### 2.5.1 Cardiac Systolic Changes

Ventricular systolic function is determined by preload, contractility, and afterload. The volume of blood in the ventricle at end diastole determines the preload on the muscle fiber, influencing the strength of ventricular contraction, and the volume of blood ejected with each beat. Contractility is an intrinsic property of the cardiac muscle fiber. Afterload is the resistance the ventricle must overcome in order to eject its volume into the peripheral circulation. Lower afterload allows a more forceful ventricular contraction with each beat. At a fixed preload and afterload, increases in contractility result in a greater cardiac output [20].

**Fig. 2.1** Regulation of fluid volume in patients with liver disease. **(a)** Normal. Arterial pressure is a function of cardiac output and peripheral vascular resistance. Cardiac output depends on venous return to the heart, which is a function of mean circulatory filling pressure. Baroreceptors regulate extracellular fluid volume in response to changes in arterial pressure. That extracellular fluid volume is in turn distributed between central and peripheral volume. **(b)** Liver disease. Decreased peripheral resistance consequent to vasodilation decreases arterial pressure. This stimulates compensatory vasoconstriction and volume retention, which increases extracellular fluid volume. Decreased albumin levels and increased vascular permeability in liver disease distribute that fluid preferentially to the extracellular compartment, so that central blood volume is decreased even in the face of increased extracellular volume. This decreased central blood volume drives a hyperdynamic state with increased cardiac output



In the cirrhotic patient there is a *resting* increase in cardiac output as part of the hyperdynamic circulation. This is thought to be due to an augmentation of both heart rate and ventricular stroke volume. Paradoxically, the cardiac response to stress may be blunted [20]. This abnormal response is not related to the effects of alcohol intake on the heart, as originally thought. Studies have demonstrated a decrease in cardiac stroke index with exercise [21].

Blunted responses have also been demonstrated with pharmacologic stressors, including angiotensin, isoproterenol, and dobutamine [20], which may be due to desensitized  $\beta$ -adrenergic receptors. In the healthy heart, chronotropic and ionotropic increases are observed in response to  $\beta$ -adrenergic stimulation. Blunting of the chronotropic response to  $\beta$ -adrenergic stimulation due to a downregulation of  $\beta$  adrenergic-receptor density has been shown in patients with liver disease [22]. In some cirrhotic patients the total duration of

electromechanical systole was prolonged due to lengthening of systolic time intervals, probably due to a reduced response to the adrenergic drive [23]. Reduced myocardial reserve and impaired oxygen extraction may be due to local imbalances of nitric oxide (NO) production and function. These changes are discussed in more detail below. Eventually, systolic function worsens with increasing liver failure. Unlike diastolic dysfunction, systolic dysfunction is not affected by ascites, and is not improved with paracentesis [23].

## 2.5.2 Cardiac Diastolic Changes

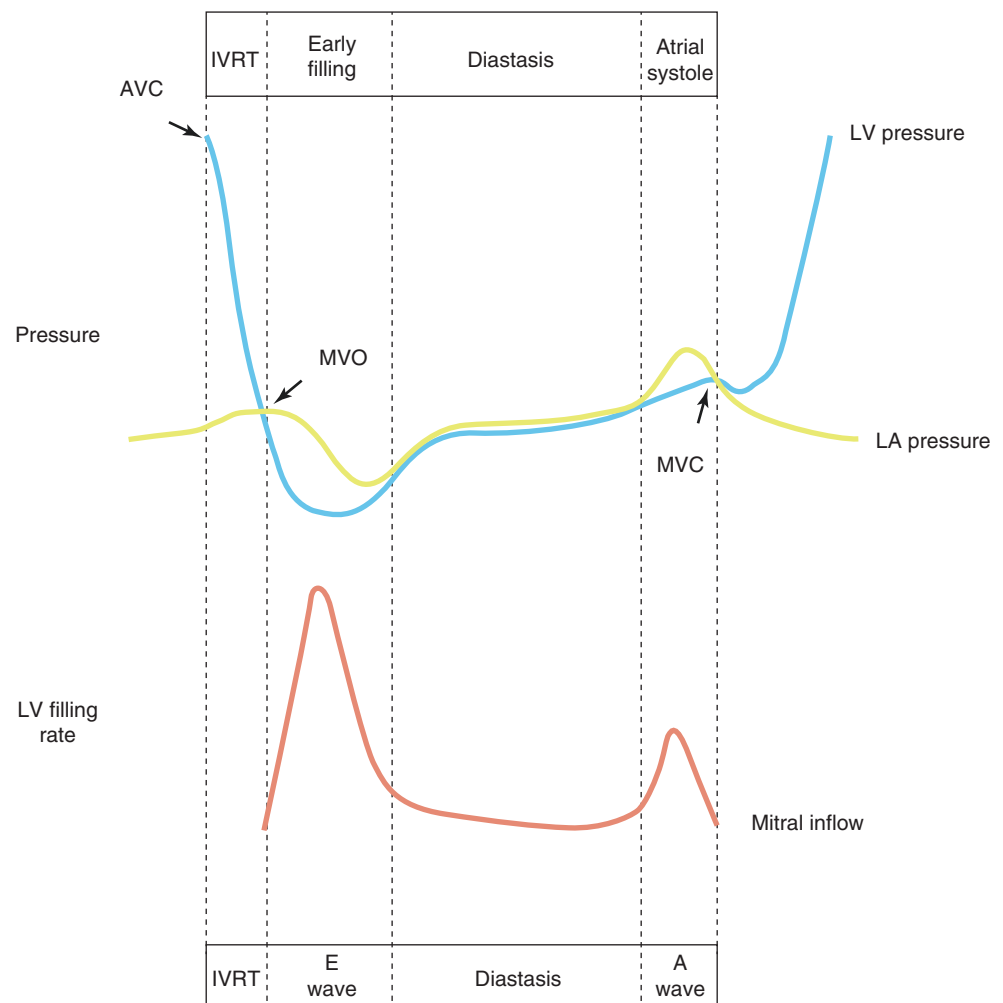
Cardiac diastolic dysfunction has been reported in cirrhotics, with post mortem analysis showing an increase in LV wall thickness, patchy fibrosis, and subendocardial edema [24]. Cirrhotics often have significant changes in diastolic filling

dynamics. Ventricular diastole is the part of the cardiac cycle when the ventricles are relaxed, and fill with blood. Diastolic filling is comprised of two parts. Early diastolic relaxation is an active process, while late diastolic filling is a passive process. The early phase relies on ventricular relaxation, elastic recoil, and passive elastic characteristics of the atrium and ventricle [20]. The late phase depends on the strength of atrial contraction and the stiffness of the ventricle. Diastolic dysfunction occurs when passive elastic properties of the myocardium are reduced due to an increase in myocardial mass and changes in the extracellular collagen [20]. This can lead to eccentric hypertrophy, with decreased compliance and higher diastolic pressures, resulting in a retrograde transmission of this pressure into the left atrium, contributing to pulmonary edema [20].

Diastolic dysfunction in chronic liver disease can be demonstrated in the absence of hypertension, coronary artery, or valvular disease [20]. This may be related to the rate of release of calcium from troponin, and the rate at which it returns to the sarcoplasmic reticulum [23]. Diastolic compliance can be measured by transthoracic echocardiography, and abnormalities are often present well before changes of systolic function are observed. Diastolic

filling is evaluated by the velocity of blood flow going from the left atrium to the left ventricle measured at the tips of the mitral leaflets during diastole. The height of the “E” wave, which represents the passive flow of blood into the ventricle with each contraction during early diastole, and is determined by the pressure gradient from the LA to the LV, is compared to that of the “A” wave in late diastole, which represents atrial contraction. There is a period of diastasis in between. At the beginning of diastole there is a fall in the LV pressure which produces an early diastolic pressure gradient from the LA, extending to the LV apex. If this drop is sufficient, the heart can fill rapidly without requiring elevated LA pressure [25]. Since LV pressure continues to drop in early diastole while its volume increases, the normal LV fills early by suction [25]. This pressure gradient may be reduced in cirrhosis and portal hypertension. During the midpoint of diastole (diastasis), the pressure between the LA and the LV equilibrates, and mitral flow nearly ceases. Late in diastole, the atrial contraction produces a second LA to LV pressure gradient that pushes blood from the LA to the LV [25]. The later A wave represents active contraction of atrial systole (see Fig. 2.2).

**Fig. 2.2** Pressures and filling rates during diastole. During isovolumic relaxation, LV pressure falls but the mitral valve remains closed. When LV pressure falls below LA pressure, the mitral valve opens. The time from AV closure to MV opening is the isovolumic relaxation time. During early filling, the pressure gradient between the LV and LA determines the LV filling rate, and is reflected in the height of the transmitral E wave. During diastasis, the LV-LA pressure gradient is low, and little filling occurs. With atrial systole, the gradient increases, and late filling occurs, as reflected in the height of the transmitral A wave





Under normal conditions, the peak early mitral velocity (E) substantially exceeds the peak velocity during the later atrial contraction (A). A lower E/A ratio, ( $<1$ ) is seen in a stiffened non-compliant ventricle [20]. This low E/A ratio is especially prominent in cirrhotics with tense ascites. Autopsy studies as early as 1957 demonstrate hypertrophy of the left ventricle in cirrhosis. In an autopsy study of 108 patients with cirrhosis, of those with no history of pathological conditions of hypertension, coronary artery disease, or valvular disease, approximately one third had cardiac hypertrophy [20]. In a study of left ventricular diastolic function in 27 cirrhotics with tense ascites, 17 cirrhotics with previous ascites, both before and after paracentesis, compared to 11 healthy controls, a significantly decreased E/A ratio was seen in cirrhotics versus controls [26]. Those with tense ascites showed the greatest degree of diastolic dysfunction. Subsequent paracentesis improved diastolic dysfunction.

Both systolic and diastolic contractile dysfunction in liver failure have been observed in other studies. Studies suggest that the extent of cirrhotic cardiomyopathy tends to worsen in concert with advancing degrees of cirrhosis [20]. In one investigation, E/A ratios were shown to be the single independent predictor of survival following transjugular intrahepatic portosystemic shunt (TIPS) insertion [27].

Diastolic dysfunction can also be assessed by tissue Doppler imaging (TDI) of movement of the mitral annulus away from the apex in early diastole, generating the diastolic mitral annular velocity ( $e'$ ); higher values represent more motion [28]. This value is a sensitive measure of ventricular diastolic function. The ratio of mitral inflow E to  $e'$  velocity ratio (E/ $e'$ ) is a dynamic marker that correlates closely with left ventricular filling patterns and can help predict heart failure events [28].

Conventional echo, Doppler and TDI have been used to characterize systolic and diastolic changes in the cirrhotic patient with portal hypertension. In a study of 60 subjects, 20 cirrhotics with ascites, 20 cirrhotics without ascites, and 20 healthy controls. Left atrial volume, E/A ratios,  $e'$  values, E/ $e'$  ratios, and Doppler deceleration times were measured. All four cardiac chambers were enlarged in cirrhotics with ascites, with LA enlargement being the most prominent. E/A velocities were mildly elevated in cirrhotic patients with or without ascites, but did not reach statistical significance. Diastolic dysfunction was diagnosed in 60% of the preascites cirrhotic patients, 80% in the cirrhotics with ascites, and 0% in the healthy controls. The E/ $e'$  ratio was the most significantly elevated in the cirrhotic patient with ascites, as compared to the other groups. Left ventricular *systolic* function was preserved in all the studied patients, reflecting robust data that diastolic abnormalities occur well before systolic dysfunction [29].

### 2.5.3 Left Ventricular Hypertrophy

Despite a decrease in cardiac afterload, left ventricular hypertrophy occurs in up to 30% of patients with advanced liver disease [30]. This hypertrophic response in cirrhotic patients may be attributable to hemodynamic overload (mechanical stress) or activation of neurohormonal pathways leading to cardiac remodeling and fibrosis [31]. Interestingly, rapid regression of left ventricular hypertrophy occurs following liver transplantation [32]. This regression of cardiomyocyte hypertrophy may be due to either alleviation of mechanical stress, reduced activation of RAAS and SNS, or, more likely, a combination of mechanisms.

### 2.5.4 Electrophysiologic Abnormalities

Prolongation of the QT interval on the electrocardiogram is well documented in patients with cirrhosis, and may be due to changes in plasma membrane fluidity and impairment of potassium ion channels [33, 34]. QT prolongation can potentially lead to ventricular arrhythmias and sudden cardiac death [35]. Moreover, QT prolongation is related to the severity of liver failure and appears to normalize with improvement in liver function following liver transplantation [36–38]. Nonetheless, the clinical significance of QT prolongation remains uncertain; ventricular tachycardia in the absence of structural heart disease in cirrhotic patients is uncommon.

Abnormal chronotropic responses to physiological and pharmacological stimuli have also been observed in cirrhotics. Many patients with cirrhosis may be tachycardic, limiting their ability to increase the heart rate further under certain physiologic states (i.e. sepsis), and impairing the ability of the heart to maintain an appropriate cardiac output for the systemic demands [39]. The interpretation of this finding, however, is uncertain. If inability to increase heart rate by the same percentage as a normal subject is due to resting tachycardia with the same peak heart rate, then while this may be characterized as chronotropic incompetence (inability to generate an increase in heart rate and thus cardiac output adequate to meet demands), the primary abnormality is the resting tachycardia rather than an inability to increase heart rate.

Cirrhotic cardiomyopathy is also associated with an increased production of natriuretic peptides. Brain natriuretic peptide (BNP) has emerged as a sensitive marker for LV dysfunction for patients with liver cirrhosis. Plasma BNP and NT-pro BNP levels are associated with the degree of cirrhosis and cardiac dysfunction [12]. Cirrhotic cardiomyopathy is also frequently associated with an increased troponin level [12].

## 2.6 Circulating Factors, Receptors, and Impaired Cardiovascular Response

A number of circulating factors affect cardiovascular responsiveness, resulting in alterations in  $\beta$ -adrenergic receptor function, muscarinic receptor function, and membrane fluidity, and all contributing to cardiac dysfunction (see Fig. 2.3).

### 2.6.1 $\beta$ -Adrenergic System

The  $\beta$ -adrenergic system consists of the adrenergic receptor, heterotrimeric guanine nucleotide-binding proteins (G-proteins), and adenylate cyclase. The stimulatory  $\beta$ -adrenergic receptor system increases heart cell contractility. Catecholamine stimulation of the  $\beta$ -adrenoceptor results in the production of the second messenger cAMP. This is the main trigger for intracellular calcium fluxes, and intracellular calcium availability is a major regulator of myocardial contractility [3]. Cyclic AMP promotes phosphorylation and activation of cellular proteins, an increase in intracellular calcium and a positive inotropic response. Muscarinic receptor stimulation exerts a negative inotropic effect on cardiac muscle, counterbalancing the stimulatory  $\beta$ -adrenergic system.

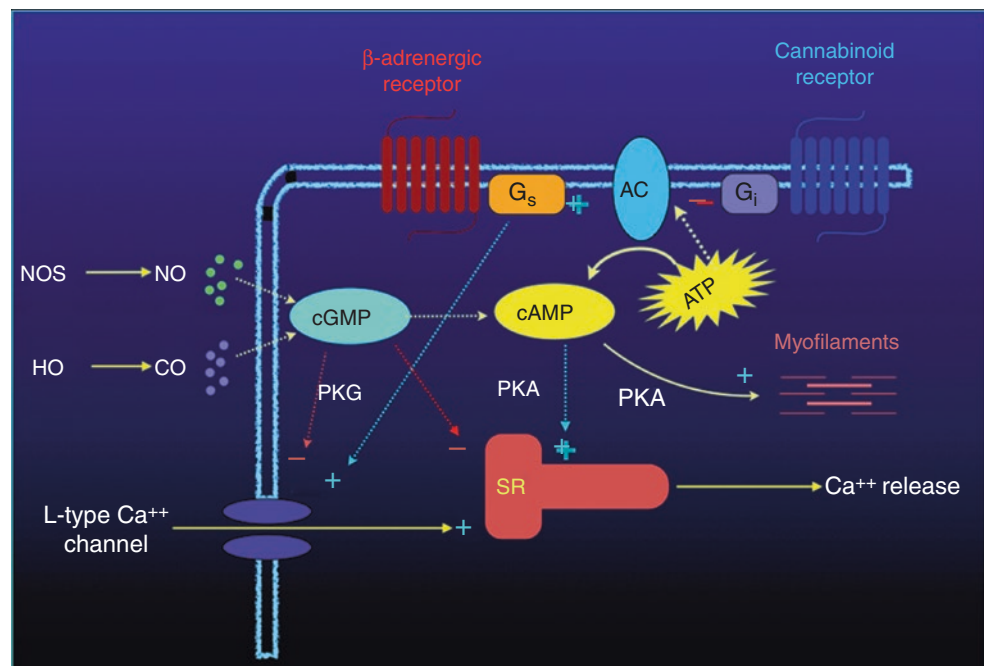
Several studies have demonstrated reduced and impaired  $\beta$ -adrenergic receptor density in cirrhotic patients [3]. Abnormal function of calcium channels with an alteration in the release of calcium may also help explain the abnormality of myocardial contraction in the cirrhotic patient [19]. Enhanced muscarinic tone in patients with

cirrhosis may also cause negative inotropic effects on the myocardium [3].

Membrane fluidity, the movement of lipid moieties in the lipid bilayer of the plasma membrane of the heart and other tissues, is reduced in the cirrhotic patient. This affects receptor-ligand interaction, receptor density and signal pathway of the  $\beta$ -adrenoceptor function. Altered membrane fluidity also affects calcium and potassium ion channels, causing changes in vascular tone. This may also affect potassium channels in ventricular myocytes which may affect the QT interval [3].

Additional circulating factors in cirrhosis and portal hypertension have been studied for more than 20 years [40]. Nitric oxide (NO) is a known vasodilator and has been identified as a major factor in arterial and splanchnic circulation. NO has a very short half-life of 20–30 s, and diffuses freely through cellular membranes, acting mainly by increasing the production of cGMP with subsequent relaxation of the smooth muscle cells. NO is synthesized by a family of three synthases, endothelial NOS (eNOS,) neuronal NOS (nNOS,) and inducible NOS (iNOS.) The synthase eNOS is calcium/calmodulin-dependent and requires cofactors for activation. It is regulated by complex protein to protein activation to ultimately generate active NO. The isoform iNOS is synthesized within several cell types, including macrophages and vascular smooth muscle cells, after induction by endotoxins and inflammatory cytokines [13]. It is released in a pulsatile manner from the beating heart and modulates the function of ion channels and transporters involved in cardiac excitation-contraction coupling [23].

**Fig. 2.3** Nitric oxide (NO), carbon monoxide (CO), endocannabinoids, and the  $\beta$ -adrenergic signal transduction pathway in cardiac cells in liver failure. *Abbreviations:* AC adenyl cyclase;  $G_s$  stimulatory G-protein complex;  $G_i$  inhibitory G-protein complex; cGMP cyclic guanosine monophosphate; ATP adenosine triphosphate; cAMP cyclic adenosine monophosphate; PKA protein kinase A; PKG protein kinase G; HO heme oxygenase; NOS nitric oxide synthase; SR sarcoplasmic reticulum





NO bioavailability is increased in patients with cirrhosis and portal hypertension, mostly because of increased activity of eNOS [2]. Upregulation of eNOS can be detected in early portal hypertension. Stimuli such as vascular endothelial growth factor, inflammatory cytokines, and mechanical shear stress stimulate the production of NO in portal hypertension leading to the development of the hyperdynamic circulatory syndrome [13]. The synthase nNOS may also be upregulated and play a role in maintaining hyperdynamic circulation [13]. Increases in shear stress may perpetuate hyperdynamic circulation by activating eNOS in the systemic circulation. In decompensated cirrhosis iNOS is upregulated within the mesentery arteries, possibly in response to inflammatory cytokines and bacterial translocation from the gut into the mesenteric lymph nodes [2].

Studies have suggested that NO plays a role in impairing cardiac pacemaker cells, contributes to a negative inotropic effect of the papillary muscles, and may inhibit cardiac function [4]. Experimental studies on cirrhotic animals reveal a link between NO and a blunted cardiac response [23].

### 2.6.2 Carbon Monoxide (CO)

Carbon monoxide (CO) an endogenously produced gas that plays a role in regulating vascular tone. CO is made by the breakdown of heme to biliverdin, through the enzyme heme oxygenase (HO). There are two isoforms of HO, HO-1 and HO-2 [13]. The HO-1 isoform has been identified in aortic and mesentery arteries of rats with biliary cirrhosis [13]. Like NO, it activates cGMP resulting in vasodilation. CO-induced vasodilation is also mediated through activation of calcium-activated potassium channels.

CO overproduction is cirrhosis favor splanchnic and arterial vasodilation. CO may also decrease ventricular contractibility due to an increase in cGMP and depressed calcium influx [23]. Although CO affects cardiac and splanchnic circulation, it has been identified as playing a more important role in hepatopulmonary changes related to cirrhosis.

### 2.6.3 Endogenous Cannabinoids (EC)

Endogenous cannabinoids (EC), also called endocannabinoids, describe a novel class of lipid signaling molecules. The most important EC is anandamide. ECs are ubiquitous and bind to the CB1 receptor in vascular endothelial cells, causing hypotension through vasodilatation [13]. There is an increase in anandamide in cirrhosis, with over-activation of the CB1 receptor located in the mesenteric vessels, causing splanchnic vasodilation and portal hypertension.

### 2.6.4 Additional Molecules

Other molecules may be involved in cirrhosis. Prostacyclin ( $\text{PGI}_2$ ) is increased in patients with cirrhosis and portal hypertension, suggesting a pathogenic role [13]. Endothelium-derived hyperpolarizing factor (EDHF) seems to be more prominent in the smaller arteries and arterioles, also contributing to vasodilation. Its role is more significant when NO is inhibited, as NO inhibits the release of EDHF [13]. Tumor necrosis factor alpha ( $\text{TNF-}\alpha$ ), activated by bacterial endotoxins, is a mediator of NO release [13].

## 2.7 Clinical Impact of Circulatory Dysfunction in Advanced Liver Disease

Despite a hyperdynamic circulatory state, patients with cirrhosis may have cardiac decompensation under conditions that challenge the cardiovascular system. These conditions may be in part due to or worsened by cirrhotic cardiomyopathy. As liver function declines, cirrhotic patients often develop refractory ascites, infection, or variceal bleeding and may require interventions such as placement of a transjugular intrahepatic portosystemic shunt (TIPS).

Patients with cirrhotic cardiomyopathy may respond poorly to these procedures and other forms of stress such as infection with abrupt alterations in cardiac hemodynamics. In particular, liver transplantation is associated with a high incidence of post-operative cardiovascular complications, including heart failure, arrhythmias, or myocardial infarction. Once the new liver is implanted, a reduction in the abnormal levels of circulating vasoactive substances occurs, decreasing the vasodilatory state that produces hyperdynamic circulation [5, 41]. The resulting increase in systemic vascular resistance and cardiac afterload, however, along with excessive fluid administration during surgery, may unmask latent cardiac dysfunction and cause pulmonary edema or overt heart failure in the immediate post-operative period.

Within 1 year following transplantation, the hyperdynamic state resolves, diastolic function improves, and the systolic response to exercise and physical stress returns to normal, suggesting that cirrhotic cardiomyopathy is completely reversible with liver transplantation [7, 32]. QT interval prolongation in cirrhosis reverses following liver transplant as well [37, 38].

Unlike liver transplantation, which reduces the high output state, insertion of a TIPS has been shown to exacerbate the hyperdynamic circulatory state of cirrhotic patients due to a sudden increase in preload caused by the increased volume load shunted to the heart [42–44]. The onset of overt heart failure following placement of TIPS has been described,

and is likely affected by the diastolic response to increased preload [45]. In one study, diastolic dysfunction was predictive of slow ascites clearance and increased mortality post-TIPS [43, 46, 47].

Intravascular volume assessments in patients with liver failure can be challenging. For example, administration of intravenous fluid boluses to improve hypotension may abruptly increase preload in an already non-compliant ventricle that is unable to increase cardiac output during stress, potentially worsening heart failure and hypotension. Measurement of central venous pressure (CVP) alone should rarely be used to make clinical decisions regarding fluid management, as left ventricular output is determined by left ventricular end diastolic pressure (LVEDP) and not right atrial pressure. Moreover, patients with tense ascites or right sided heart failure may have an elevated CVP in the presence of volume depletion due to increased intra-abdominal pressure or elevated right heart pressures. In these situations, continuous hemodynamic monitoring of cardiac output and filling pressures can help guide titration of volume expanders, inotropes, or vasopressors.

When congestive heart failure predominates, treatment options are similar to those with non-cirrhotic cardiac dysfunction—with one important exception. Most patients with cirrhosis have low arterial blood pressures as a result of peripheral vasodilation and therefore may not tolerate drugs that reduce preload or afterload [20]. Decreases in blood pressure due to inotropic drugs with vasodilatory properties such as dobutamine and milrinone may induce a precipitous fall in blood pressure in hepatic patients by causing further vasodilatation. The response to dobutamine may also be blunted in patients with cirrhosis due to  $\beta$ -adrenergic receptor down-regulation. Thus norepinephrine, a potent vasoconstrictor with some inotropic effect, may be preferred when treating patients with cardiogenic shock and hypotension.

Managing patients with cirrhosis and cardiac dysfunction may be challenging and often requires a multidisciplinary team approach [47].

## Conclusion

The principle hemodynamic abnormality in patients with cirrhosis and portal hypertension is systemic vasodilation with a hyperdynamic circulatory syndrome in which cardiac output and heart rate are increased and systemic vascular resistance is decreased. This is mediated by both structural changes in the splanchnic circulation that decrease circulating blood volume and humoral changes with release of several vasoactive substances that decrease arterial tone in the systemic circulation. Despite this hyperdynamic circulatory state, the heart may not be normal; careful investiga-

tion has revealed a number of cardiovascular abnormalities, including diastolic dysfunction, blunted systolic response to stress, and electrophysiologic abnormalities, which together have been termed ‘*cirrhotic cardiomyopathy*.’ These abnormalities may not be apparent at rest, but may decrease cardiac reserve and become manifest during periods of hemodynamic stress. Accumulating evidence suggests that cirrhosis-related cardiovascular abnormalities play a major role in the pathogenesis of several complications of liver disease, including hepatorenal syndrome, ascites, spontaneous bacterial peritonitis, gastroesophageal varices, and hepatopulmonary syndrome.

## References

1. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest.* 1953;32(10):1025–33.
2. Bolognesi M, Di Pascoli M, Verardo A, Gatta A. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. *World J Gastroenterol.* 2014;20(10):2555–63.
3. Al-Hamoudi WK. Cardiovascular changes in cirrhosis: pathogenesis and clinical implications. *Saudi J Gastroenterol.* 2010;16(3):145–53.
4. Martell M, Coll M, Ezkurdia N, Raurell I, Genesca J. Physiopathology of splanchnic vasodilation in portal hypertension. *World J Hepatol.* 2010;2(6):208–20.
5. Møller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J.* 2013;34(36):2804–11.
6. Krag A, Bendtsen F, Burroughs AK, Møller S. The cardiorenal link in advanced cirrhosis. *Med Hypotheses.* 2012;79(1):53–5.
7. Yang YY, Lin H-C. The heart: pathophysiology and clinical implications of cirrhotic cardiomyopathy. *J Chin Med Assoc.* 2012;75:619–23.
8. Pendyal A, Gelow JM. Cardiohepatic interactions: implications for management in advanced heart failure. *Heart Fail Clin.* 2016;12(3):349–61.
9. Ishibashi H, Nakamura M, Komori A, Migita K, Shimoda S. Liver architecture, cell function, and disease. *Semin Immunopathol.* 2009;31(3):399–409.
10. Lautt WW. Hepatic circulation physiology and pathophysiology. Morgan & Claypool Lifesciences: San Rafael, CA; 2010.
11. Rappaport AM, Borowy ZJ, Loughheed WM, Lotto WN. Subdivision of hexagonal liver lobules into a structural and functional unit; role in hepatic physiology and pathology. *Anat Rec.* 1954;119(1):11–33.
12. Pudil R, Pelouch R, Praus R, Vasatova M, Hulek P. Heart failure in patients with liver cirrhosis. *Cor Vasa.* 2013;55(4):e391–e6.
13. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology.* 2006;43(2 Suppl 1):S121–31.
14. Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J Hepatol.* 1985;1(4):325–37.
15. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol.* 2000;32(1 Suppl):141–56.
16. Møller S, Gulberg V, Henriksen JH, Gerbes AL. Endothelin-1 and endothelin-3 in cirrhosis: relations to systemic and splanchnic haemodynamics. *J Hepatol.* 1995;23(2):135–44.
17. Abralde JG, Iwakiri Y, Loureiro-Silva M, Haq O, Sessa WC, Groszmann RJ. Mild increases in portal pressure upregulate vascu-

- lar endothelial growth factor and endothelial nitric oxide synthase in the intestinal microcirculatory bed, leading to a hyperdynamic state. *Am J Physiol Gastrointest Liver Physiol.* 2006;290(5):G980–7.
18. Gould L, Shariff M, Zahir M. Cardiac hemodynamics in alcoholic patients with chronic liver disease and a presystolic gallop. *J Clin Invest.* 1969;48(4):754–60.
  19. Sawant P, Vashishtha C, Nasa M. Management of cardiopulmonary complications of cirrhosis. *Int J Hepatol.* 2011;2011:280569.
  20. Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. *Best Pract Res Clin Gastroenterol.* 2007;21(1):125–40.
  21. Kelbaek H, Eriksen J, Brynjolf I, Raboel A, Lund JO, Munck O, et al. Cardiac performance in patients with asymptomatic alcoholic cirrhosis of the liver. *Am J Cardiol.* 1984;54(7):852–5.
  22. Lee SS, Marty J, Mantz J, Samain E, Braillon A, Lebrec D. Desensitization of myocardial beta-adrenergic receptors in cirrhotic rats. *Hepatology.* 1990;12(3 Pt 1):481–5.
  23. Zardi EM, Abbate A, Zardi DM, Dobrina A, Margiotta D, Van Tassel BW, et al. Cirrhotic cardiomyopathy. *J Am Coll Cardiol.* 2010;56(7):539–49.
  24. Timoh T, Protano MA, Wagman G, Bloom M, Vittorio TJ. A perspective on cirrhotic cardiomyopathy. *Transplant Proc.* 2011;43(5):1649–53.
  25. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. *Circulation.* 2009;120(9):802–9.
  26. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology.* 1997;26(5):1131–7.
  27. Cazzaniga M, Salerno F, Pagnozzi G, Dionigi E, Visentin S, Cirello I, et al. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. *Gut.* 2007;56(6):869–75.
  28. Abraham TP, Dimaano VL, Liang HY. Role of tissue Doppler and strain echocardiography in current clinical practice. *Circulation.* 2007;116(22):2597–609.
  29. Dadhich S, Goswami A, Jain VK, Gahlot A, Kulamarva G, Bhargava N. Cardiac dysfunction in cirrhotic portal hypertension with or without ascites. *Ann Gastroenterol.* 2014;27(3):244–9.
  30. Batra S, Machicao V, Bynon JS, Mehta S, Tanikella R, Krowka MJ, Zacks S, Trotter J, Roberts KE, Brown RS, Kawut SM, Fallon MB, Pulmonary Vascular Complications of Liver Disease Group. The impact of left ventricular hypertrophy on survival in candidates for liver transplantation. *Liver Transpl.* 2014;20(6):705–12.
  31. De Marco M, Chinali M, Romano C, Benincasa M, D'Addeo G, D'Agostino L, deSimone G. Increased left ventricular mass in pre-liver transplantation cirrhotic patients. *J Cardiovasc Med (Hagerstown).* 2008;9(2):142–6.
  32. Torregrosa M, Aguadé S, Dos L, Segura R, González A, Evangelista A, Castell J, Margarit C, Esteban R, Guardia J, Genescà J. Cardiac alterations in cirrhosis: reversibility after liver transplantation. *J Hepatol.* 2005;42(1):68–74.
  33. Ward CA, Ma Z, Lee SS, Giles WR. Potassium currents in atrial and ventricular myocytes from a rat model of cirrhosis. *Am J Physiol Gastrointest Liver Physiol.* 1997;273(2):537–44.
  34. Møller S, Henriksen J. Cirrhotic cardiomyopathy a pathophysiological review of circulatory dysfunction in liver disease. *Heart.* 2002;87:9–15.
  35. Day CP, James O, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet.* 1993;341(8858):1423–8.
  36. Bernardi M, Galandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: Prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology.* 1998;27(1):28–34.
  37. Mohamed R, Forsey P, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. *Hepatology.* 1996;23(5):1128–34.
  38. García González M, Hernandez-Madrid A, Lopez-Sanromán A, Candela A, Nuño J, Barcena R. Reversal of QT interval electrocardiographic alterations in cirrhotic patients undergoing liver transplantation. *Transplant Proc.* 1999;31(6):2366–77.
  39. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. *J Hepatol.* 2006;44(5):994–1002.
  40. Whittle BJ, Moncada S. Nitric oxide: the elusive mediator of the hyperdynamic circulation of cirrhosis? *Hepatology.* 1992;16(4):1089–92.
  41. Therapondos G, Flapan A, Plevris JN, Hayes PC. Cardiac morbidity and mortality related to orthotopic liver transplantation. *Liver Transplant.* 2004;10:1441–53.
  42. Azoulay D, Castaing D, Dennison A, Martino W, Eyraud D, Bismuth H. Transjugular intrahepatic portosystemic shunt worsens the hyperdynamic circulatory state of the cirrhotic patient: preliminary report of a prospective study. *Hepatology.* 1994;19(1):129–32.
  43. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol.* 2015;28(1):31–40.
  44. Merli M, Valeriano V, Funaro S, Attili AF, Masini A, Efrati C, De Castro S, Riggio O. Modifications of cardiac function in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt (TIPS). *Am J Gastroenterol.* 2002;97(1):142–8.
  45. Braverman AC, Steiner M, Picus D, White H. High-output congestive heart failure following transjugular intrahepatic portal-systemic shunting. *Chest.* 1995;107:1467–9.
  46. Rabie RN, Cazzaniga M, Salerno F, Wong F. The use of E/A ratio as a predictor of outcome in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. *Am J Gastroenterol.* 2009;104:2458–66.
  47. Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, et al. Intensive care of the patient with cirrhosis. *Hepatology.* 2011;54(5):1864–72.

Paul Bergl and Jonathon D. Truwit

## Abstract

In this chapter, we will discuss hepatic-pulmonary pathophysiologic interactions in acute and chronic liver disease. Most of our understanding of how liver disease compromises the key functions of the respiratory system comes from studies of physiologic extremes. From these data, we can infer how milder manifestations of liver disease may contribute to abnormalities in ventilation and gas exchange. In liver disease, it is well established that optimal ventilation is most often perturbed by altered respiratory mechanics from ascites, hydrothorax, and hepatic cachexia. Ventilation-perfusion (V-Q) mismatching may be caused or worsened by compressive atelectasis from ascites or hydrothorax, imbalanced matching in hepatopulmonary syndrome, dynamic small airway collapse from increased pulmonary blood flow, or any of the various causes typically seen in hypoxemic hospitalized patients. Diffusion abnormalities also have myriad causes, and a low diffusion capacity (DLCO) without alternative explanation may represent the uncommon but well characterized hepatopulmonary syndrome. Additionally, acute liver failure may be complicated by the acute respiratory distress syndrome (ARDS), which itself hampers respiratory mechanics, V-Q matching, and gas diffusion. Patients with chronic liver disease are also at risk for ARDS as they are prone to sepsis and aspiration pneumonitis. Managing ARDS in these populations requires special consideration of extra-hepatic complications of liver failure such as elevated intracerebral pressure and tense ascites.

## Keywords

Liver disease • Respiratory physiology • Pulmonary function tests • Respiratory mechanics  
Lung compliance • DLCO • Acute respiratory distress syndrome • Acute liver failure

## Abbreviations

ARDS Acute respiratory distress syndrome  
COPD Chronic obstructive pulmonary disease  
DLCO Diffusion capacity of lungs for carbon monoxide

HPS Hepatopulmonary syndrome  
MELD Model for end-stage liver disease (score)  
 $P_{CO_2}$  Partial pressure of carbon dioxide  
 $P_{ACO_2}$  Alveolar partial pressure of carbon dioxide  
 $P_{aCO_2}$  Arterial partial pressure of carbon dioxide  
 $P_{AO_2}$  Arterial partial pressure of oxygen  
 $P_{aO_2}$  Arterial partial pressure of oxygen  
PEEP Positive end-expiratory pressure  
V-Q Ventilation-perfusion

P. Bergl, M.D.  
Department of Medicine, Medical College of Wisconsin,  
Milwaukee, WI, USA  
e-mail: [pbergl@mcw.edu](mailto:pbergl@mcw.edu)

J.D. Truwit, M.D., M.B.A. (✉)  
Froedtert and the Medical College of Wisconsin,  
Milwaukee, WI, USA  
e-mail: [Jonathon.truwit@froedtert.com](mailto:Jonathon.truwit@froedtert.com)

## Lung Volumes and Capacities

ERV	Expiratory reserve volume
FEV1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
TLC	Total lung capacity
RV	Residual volume
VC	Vital capacity

### Learning Objectives

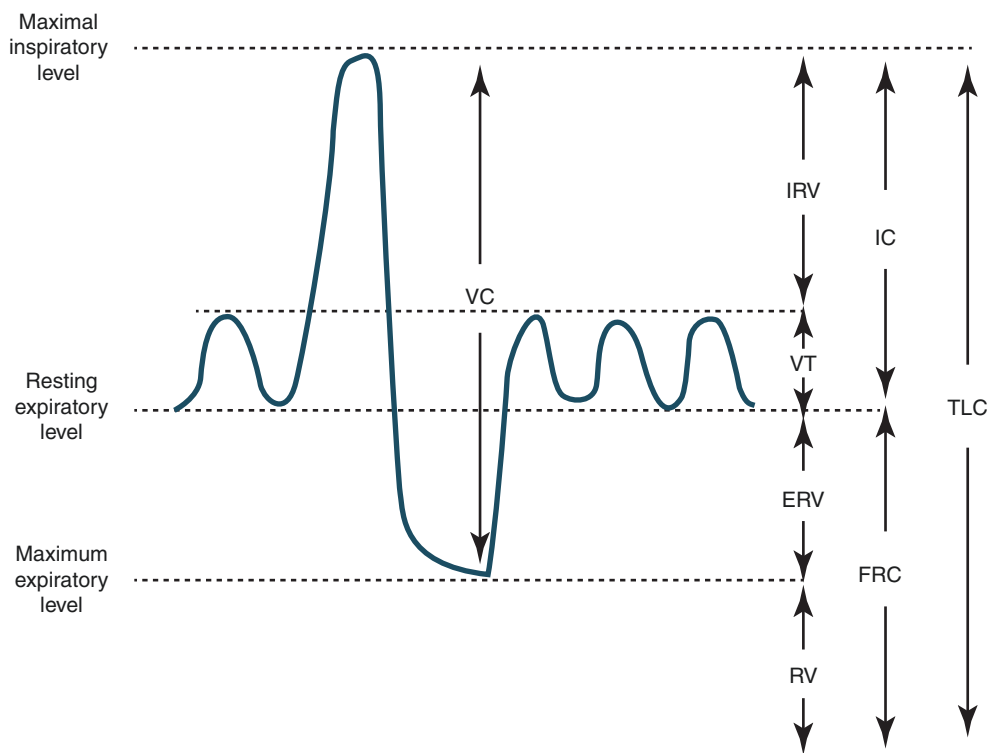
By the end of this chapter, learners will be able to:

- Describe the pathophysiologic mechanism of restrictive and obstructive defects seen on pulmonary function tests of patients with liver disease
- List the mechanisms of the restrictive spirometric pattern in patients with liver disease and contributors to poor respiratory system compliance in this population
- Predict changes in lung volumes, lung capacities, and respiratory system compliance after large volume paracentesis
- Recognize the impact of neuromuscular weakness in pulmonary function of patients with liver disease
- Explain why DLCO is commonly reduced in cirrhotic patients with and without the hepatopulmonary syndrome
- Articulate the physiologic tenets of managing acute respiratory distress syndrome in patients with acute and chronic liver disease

## 3.1 A Primer on Clinical Assessment of Pulmonary Physiology [1–4]

Because an understanding of ventilation first requires working knowledge of measured lung volumes, lung capacities, and results of basic spirometric tests, we will first briefly review these critical concepts. Total lung capacity (TLC) is the maximal air-holding capacity of the lungs (Fig. 3.1). There are four end-expiratory volumes and capacities of clinical relevance: vital capacity (VC), functional residual capacity (FRC), residual volume (RV), and expiratory reserve volume (ERV). VC reflects the volume of air exhaled after maximal inspiratory effort; VC can be measured during forced exhalation (i.e. the forced vital capacity, FVC) or can be derived from other measurements made during formal lung volume testing (the so-called slow vital capacity, SVC). FRC reflects the volume of air in the lungs at end-expiration in resting tidal breathing and is subdivided into the ERV and RV. The RV is the volume of air in the lungs at the end of maximal expiratory effort and thus represents the minimum volume of gas that is ever contained in the lungs *in vivo*. Except for FVC and SVC, all of these measures require formal testing in a pulmonary function lab using body plethysmography or gas dilution techniques [5].

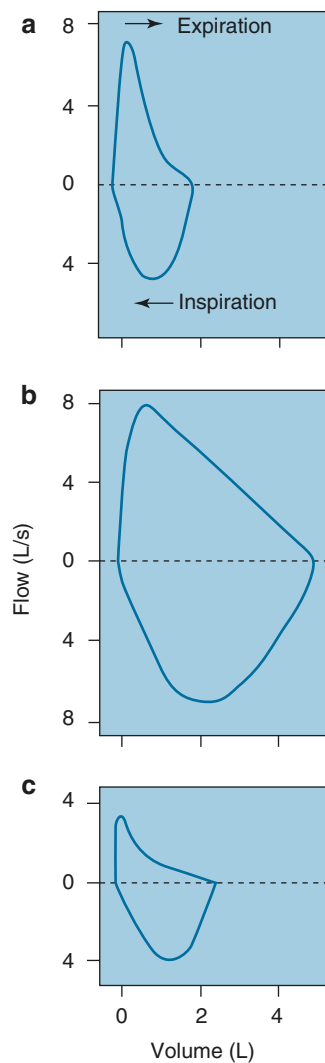
Spirometry is a simple but powerful means of quantifying lung function, and many of the available data on pulmonary complications of liver disease use spirometric measurements. The two most important measurements in spirometry are the forced expiratory volume in one second (FEV1) and



**Fig. 3.1** Lung volumes and capacities. See the body of the text for definitions. From *Murray & Nadel's Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. (Figure 25-2). Reprinted with permission from the publisher



the FVC. From these two metrics, one of three patterns of lung function emerges: normal, obstructive, restrictive (Fig. 3.2) with some patients exhibiting a mixed pattern of obstruction and restriction. An obstructive defect is classified when the ratio of FEV1/FVC is  $<70\%$  while a restrictive pattern is suggested by FVC  $<80\%$  predicted without airflow obstruction [6]. However, by convention, restrictive lung disease requires formal assessment of TLC [5] because only about 60% of patients with a restrictive defect on spirometry have true restriction by TLC measurement, in particular for patients with reduced FEV1/FVC [7].



**Fig. 3.2** The three common spirometric patterns. A normal flow-volume loop is centered (b). Restrictive pulmonary disorders are characterized by lower lung volumes and higher lung elastic recoil, thus giving a higher-than-expected flow rate at a given lung volume (a). Obstructive defects are characterized by diminished expiratory flows and often a concave expiratory limb, reflecting distal airway obstruction (c). From Murray & Nadel's *Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. (Figure 25-15). Reprinted with permission from the publisher

### 3.2 Lung Volumes and Capacities in Liver Disease

Ventilatory defects are relatively common in patients with cirrhosis [8] and—though most commonly associated with concomitant ascites—are not exclusive to patients with ascites. For example, in patients undergoing liver transplantation, restrictive defects have a strong tendency to improve from pre-transplant values, even in patients without ascites [8], suggesting liver disease and its consequences are causative and not merely an association. Ascites predictably causes a significant reduction in FVC, FRC, and TLC [9–11] and a strong tendency toward the restrictive pattern on spirometry [12–14]. Hepatic hydrothorax similarly produces a restrictive spirometric pattern [14]. With increasing intra-abdominal hydrostatic pressure, such as seen in ascites, FVC, FRC, and TLC diminish further [12, 15]; thus, increasingly tense ascites is modestly correlated with worsening restrictive physiology [10, 12]. When patients with ascites lie supine, FVC diminishes [11], and FRC and TLC may also significantly decrease [12]. As expected, large volume paracentesis reliably improves measures of pulmonary function including FVC, FRC, and TLC [11, 16–19] in addition to providing relief from dyspnea and improving oxygenation. While ventilated patients have been less frequently studied, therapeutic paracentesis effectively increases end-expiratory lung volume [14, 20], a reasonable surrogate for FRC in ventilated patients with acute lung injury [21]. However, even after substantial fluid removal, patients may not reach normalization of lung volumes due to residual ascites, muscular weakness, or interstitial pulmonary edema. Similar to therapeutic paracentesis, aggressive diuresis also significantly improves FVC, FRC, and TLC in patients with ascites [19].

While ascites represents an obvious contributor to restrictive physiology in patients with chronic liver disease, more subtle respiratory disorders have been appreciated in patients with hepatic steatosis and chronic liver disease. Population-based studies of patients with non-alcoholic fatty liver disease (NAFLD) have found links between the severity of hepatic steatosis and the restrictive pattern on spirometry in pulmonary function tests [22, 23]. Using data from the Third National Health and Nutrition Examination Survey (NHANES III), one group of investigators identified significant trends in increased prevalence of the restrictive pattern on spirometry with worsening degrees of hepatic steatosis [22]. This association persisted even after adjustment for multiple confounders such as waist circumference, level of physical activity, and smoking. A similar trend was seen in a population-based cross-sectional study in Korea [23]. Again, after controlling for body mass index and other parameters of cardiometabolic risk, investigators found that FVC and FEV1 were inversely correlated to the severity of

hepatic steatosis. The mechanisms of these associations and are not entirely clear; hepatic steatosis and restrictive spirometric patterns may be epiphenomena of underlying pathophysiologic processes like abdominal adipose distribution [24], insulin resistance [25], or low-grade chronic systemic inflammation [26]. In patients with chronic hepatitis or Childs-Pugh class A and B cirrhosis who lack significant cardiopulmonary comorbidities, the severity of liver disease also appears to be significantly and inversely correlated with abnormalities in FVC [27]. However, when these patients are subjected to formal lung volume testing, very few have restrictive lung disease by this standard. Other data suggest that while restrictive defects on spirometry are common in cirrhosis, only a minority of patients have true restriction when TLC is measured [28].

Taken together, these data affirm that restrictive spirometric patterns are more common in patients with chronic liver disease than in the general population, but the majority of patients with chronic hepatitis and compensated cirrhosis do not exhibit a significant restrictive defect on testing of lung volumes. Nonetheless, a restrictive pattern on spirometry is linked to poor exercise tolerance and dyspnea and thus should not be discounted as a normal variant in these populations [29]. Furthermore, the restrictive spirometry pattern predicts post-operative pneumonia and respiratory failure in patients undergoing liver transplantation, so it has important prognostic value in liver disease [14].

Obstructive defects on spirometry are less commonly observed in non-smoking cirrhotic patients though specific disorders characterized by concomitant liver and pulmonary disease, such as alpha-1 antitrypsin deficiency (A1ATD) and cystic fibrosis (CF), are expected to be accompanied by obstructive lung physiology. The presence of concomitant liver disease in these populations does not appear to appreciably increase the risk of airway obstruction. While CF patients undergoing liver transplantation have a tendency toward lower FEV1 than CF patients without substantial liver disease, some of these differences are attenuated during the medical optimization leading up to surgery [30]. Furthermore, liver transplantation does not have a clinically significant effect on obstruction as measured by FEV1 in CF patients. Similarly, patients with the ZZ phenotype of A1AT do not experience a significant improvement in FEV1 after liver transplantation [31].

Cross-sectional studies of unselected cirrhotic patients have shown an increased prevalence of the obstructive pattern on spirometry, even in the absence of pre-existing lung disease [8, 9]. This finding however is not consistent across all studies of pulmonary function in cirrhosis [28, 32], so an increased prevalence of obstructive patterns in some of these populations may simply reflect undiagnosed pulmonary disease. To date, there has been no plausible, definite physiologic explanation for large airway obstruction in liver

disease, so any increased risk of obstructive defects on spirometry in patients with liver disease likely derives from non-hepatic factors. Furthermore, because FEV1 not significantly improve after transplantation in CF and A1AT patients, we can conclude that liver disease does not cause large airway obstructive lung disease *per se*.

It is worth noting that obstructive physiology in the lung may not be captured exclusively by measuring the ratio of FEV1/FVC, the current gold standard for obstruction [5]. FEV1 reflects airflow limitation in large airways, but obstruction can occur from airway collapse later during forced expiration. Indeed, the predominant mechanism for airflow obstruction in patients with cirrhosis—and also one of the mechanisms of V-Q mismatch, as discussed in the following chapter—is small airway closure from hemodynamic alterations such as increased pulmonary blood flow and interstitial edema [32–35]. Traditionally small airway closure is identified through spirometric measurements like the maximal forced expiratory flow at various percentages of FVC (e.g. the commonly reported  $FEF_{25-75\%}$  in pulmonary function tests) or measurement of the closing volume [3, 6]. Closing volume is the point at which basilar small airways close and is typically quantified as a percentage of the vital capacity. In healthy individuals, the closing volume should exceed FRC; otherwise, small airways will experience collapse even during tidal breathing [3]. Several investigators have documented markedly elevated closing volumes in cirrhosis [32, 35–37], especially in those patients with arterial hypoxemia [32], and frequently these closing volumes exceed FRC. Additionally, in cirrhotic patients with a normal FEV1, at least one group of investigators has demonstrated a significant reduction in  $FEF_{25\%}$  relative to  $FEF_{50\%}$  and FEV1 [32], a finding that supports dynamic small airway obstruction as the lung volumes approach FRC. Ascites probably contributes an additional tendency toward small airway collapse, with patients having significantly lower  $FEF_{25-75\%}$  when compared to cirrhotic patients without ascites [13].

Despite the presence of dynamic small airway disease in cirrhotic patients, the clinical relevance of these findings is open to interpretation. Small airway closure contributes to V-Q mismatch and arterial hypoxemia (see discussions later in this chapter as well as the following chapter), but it may not correlate to meaningful changes in lung function, dyspnea, or exercise tolerance in these populations. Though small airway obstruction likely contributes to some of the symptoms and clinical manifestations of asthma and chronic obstructive pulmonary disease (COPD) [38], optimal treatment of small airway obstruction even in these well studied disorders has a nascent and evolving evidence basis [39, 40]. Moreover, liver disease is one of the least well characterized disorders of small airway obstruction [41]. Thus, the findings of mild small airway obstruction in liver disease may primarily be of academic interest. Given the available data, liver





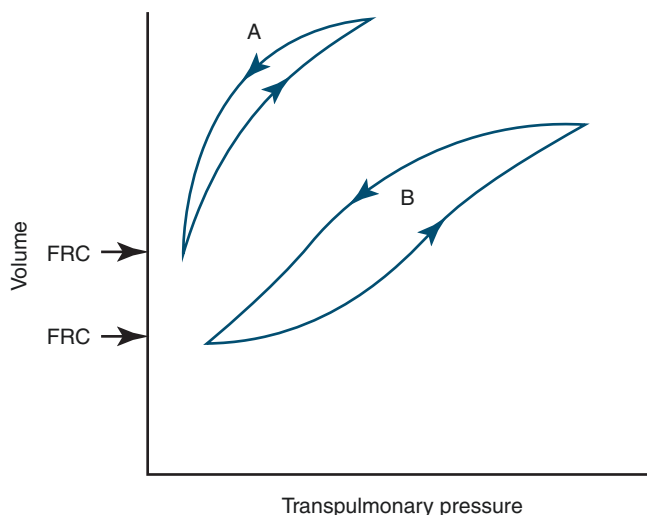
between ascites and the severity of restrictive defect on spirometry are predictable from an understanding of respiratory system compliance. Measurements of the FVC rely not only on airway resistance and respiratory effort, but also on the lung's elasticity and tendency toward collapse [42]. Elastic recoil forces—and thus expiratory flows—are greatest when the lungs are stretched to TLC. However, when patients are tidal breathing closer to their RV—i.e. when FRC and ERV decrease—then expiratory flow is limited [43], reflected as a lower FVC. The effect of ascites on lowering FRC puts the lungs at a mechanical disadvantage by lowering the elastic recoil potential. In addition, FRC roughly correlates with lung compliance, so the finding of a low FRC in ascites is unsurprising. Recall that at FRC, the lung's tendency to collapse perfectly balances the chest wall's tendency to expand. With disease processes that cause lung volumes to decrease and/or reduce lung compliance, FRC will accordingly decrease [1]. Furthermore, lung compliance during inspiration decreases with reduced lung volumes as predicted by the compliance curves in inspiration and expiration (i.e. lung hysteresis) (Fig. 3.4); thus, any factor that decreases lung volumes will reduce lung compliance [1].

Massive increases in intra-abdominal pressure are known to have deleterious effects respiratory system compliance [44]. Abdominal distention accompanied by increased intra-abdominal pressure primarily exhibits its negative effect on the respiratory system by reducing compliance of the chest wall [11, 15, 45, 46]. A long-held belief is that ascites fixes the diaphragm and abdominal wall into a static position, and the less compliant thoracic cage must be overcome to inspire

[11]. This notion is supported by the observation that FRC remains relatively unaffected when moving from sitting to the supine position when intra-abdominal hydrostatic pressures are especially high [12]. Because FRC itself is a marker of abdominal compliance [12], we can infer that the abdominal wall compliance is relatively fixed in tense ascites irrespective of body position. In addition, patients with ascites exhibit higher levels of intrinsic positive end expiratory pressure (PEEP<sub>i</sub>) [47], a finding consistent with the hypothesis of small airway closure discussed previously. As patients must generate a more negative intrapleural pressure to overcome the inertia of PEEP<sub>i</sub> in order to inflate the lungs, PEEP<sub>i</sub> represents another mechanical load on the respiratory system [48] and another contributor to poor respiratory system compliance in patients with ascites.

During tidal breathing, patients with massive ascites exhibit large swings in pleural pressures while having little change in intra-abdominal pressure [47]. Not only do these findings corroborate the reliance on chest wall movement and the relative fixation of the abdominal compartment in tense ascites, but they also demonstrate that ascites represents a state of increased work of breathing. This increased mechanical work is reflected by abnormally large swings in pleural pressure and transdiaphragmatic pressure required even during quiet breathing [47]. With positive pressure mechanical ventilation, the patient with ascites would theoretically experience reduced work of breathing, and positive pressure could potentially improve compliance for a given tidal volume by alveolar recruitment. However, respiratory system compliance declines markedly with increasing intra-abdominal pressure even during positive pressure ventilation [46, 49], and the most significant effects occur when intra-abdominal pressure exceeds PEEP by 15 mmHg or more [46]. Because the mechanical load of ascites is preferentially transferred during the inspiratory cycle, clinician should feel confident in using the plateau pressure in mechanically ventilated patients with ascites to characterize the severity of the decrease in chest wall and abdominal compliance [46].

Large volume paracentesis predictably leads to marked improvement in pulmonary compliance. For spontaneously breathing patients, pleural pressure swings improve dramatically after fluid removal and are directly related to the volume of fluid removed [47]. Thus, as discussed previously, the improvement in FRC, TLC, and FRV after large volume paracentesis reflect improved respiratory system compliance and reduced work of breathing. In mechanically ventilated patients with ascites, paracentesis improves compliance immediately [20, 49], and this effect may be durable at least 6 h after the procedure [20, 49]. Drops in plateau pressure after paracentesis are nearly proportional to gains in respiratory system compliance and can thus be used as a marker at the bedside. Because the abdomen can accommodate large amounts of fluid before intra-abdominal pressure rises, only



**Fig. 3.4** Hysteresis in lung. The pressure-volume relationship of the lung (i.e. compliance) varies between the inspiratory and expiratory limb due to differential effects of surfactant on surface tension. The acutely injured lung (A) displays differing hysteresis curves from the normal healthy lung (B). From Murray & Nadel's *Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. (Figure 5-8). Reprinted with permission from the publisher

small amounts of fluid removal (about 200 mL) may be required to reduce intra-abdominal hydrostatic pressure and improve respiratory system compliance [12]. Practically speaking though, clinicians should target the largest volume of ascites that can be feasibly removed.

Hepatic hydrothorax and interstitial pulmonary edema are two other contributors to poor respiratory system compliance described in liver disease. Though respiratory system compliance has not been studied specifically in hepatic hydrothorax, it presumably behaves similarly to other transudative pleural effusions in reducing respiratory system compliance by adding a mechanical load to the chest wall. The presumed mechanism of hepatic hydrothorax is transdiaphragmatic migration of ascitic fluid [50]. The compensatory large transpleural pressure swings seen in ascites that we previously discussed theoretically could contribute to hepatic hydrothorax as significant drops in intrapleural pressure would encourage transdiaphragmatic fluid shifts, thus creating a vicious cycle of worsening dyspnea, increased work of breathing, and worsening chest wall compliance. At this point, this mechanism is purely speculative, as there are no human or animal studies to verify this physiology.

While frequently discussed as a potential complication of anasarca from cirrhosis, interstitial pulmonary edema appears to be a relatively uncommon finding in unselected cirrhotic patients [51]. In animal models, the development of cirrhosis appears to be accompanied by a propensity for mild interstitial edema and trivial increases in lung water [52]. Interstitial edema in itself may not be a major contributor to poor lung compliance; instead increased pulmonary blood volume and alveolar edema seem to be the culprits [53, 54]. Since increased pulmonary vascular blood volume and hyperdynamic circulation with increased cardiac output are features of hepatopulmonary syndrome [55, 56], reduced lung compliance should be expected. Once patients with liver disease have readily apparent pulmonary edema (by clinical examination or chest radiography), they should be assumed to have markedly reduced pulmonary compliance [54].

### 3.4 Neuromuscular Strength and Exercise Tolerance in Liver Disease

Advanced chronic liver disease is often accompanied by cachexia, skeletal muscle wasting, and accordingly respiratory muscle weakness. These changes are identified by lower maximum expiratory and inspiratory pressures (MEP and MIP) on pulmonary function testing, two tests that predominantly reflect muscular strength [57]. Not surprisingly, mild to moderate abnormalities in MEP and MIP are frequently encountered in cirrhotic patients awaiting transplantation [28] but are less consistently identified in patients with milder cirrhosis [58]. Inspiratory muscle strength (as

measured by MIP) may be nearly halved in patients with severe liver disease [28] and correlates strongly with overall dyspnea in this population [59]. When compared to patients with Childs-Pugh class A or B cirrhosis, Childs Pugh class C patients have more significant reductions in respiratory muscle strength [60]. Similarly, higher MELD scores are tightly correlated with inspiratory muscle weakness [61]. The presence of ascites has been shown to have an inconsistent effect on inspiratory muscle strength [47, 59]. Recent evidence supports the role of adynamia of the diaphragm and rectus abdominus, and not non-muscular factors, as key determinants of respiratory strength in cirrhotic patients [62]. Recognizing the prevalence of neuromuscular respiratory weakness in liver disease is particularly relevant in the intensive care unit because inspiratory muscle weakness is a key predictor of failure to wean from mechanical ventilation [63–65]. The MIP is an important prognostic marker in liver disease as well; patients with poor neuromuscular strength have significantly worse survival after liver transplantation [66].

### 3.5 Regulation of Ventilation and Maintenance of Acid-Base Neutrality

In healthy individuals, ventilation is regulated by the brainstem breathing centers, a complex network of interconnected neurons within the medulla and, to a lesser extent, the pons [1, 67]. These neurons generate efferent breathing signals to the respiratory muscles while also reflexively incorporating feedback from afferent pathways including the pontine respiratory group, central and peripheral chemoreceptors, stretch receptors in the lung and diaphragm, and the cerebral cortex. The feedback loops also regulate ventilation, but the central chemoreceptors' response to extracellular pH within the cerebrospinal fluid—itsself a reflection of arterial  $P_{CO_2}$ —is the most powerful regulator of breathing.

Regulation of ventilation is commonly perturbed in chronic liver disease; patients exhibit primary hyperventilation with hypocapnia and compensated respiratory alkalosis. Historically, hyperventilation was in part ascribed to compensation for concomitant mild arterial hypoxemia [68]. However, multiple studies have documented hyperventilation in chronic liver disease even in the absence of hypoxia and underlying cardiopulmonary comorbidity [69–73]. Similar observations about hyperventilation have also been observed in comatose patients with acute liver failure [74]. In chronic liver disease, the degree of hyperventilation—as manifested by lower  $P_{CO_2}$ —generally correlates with the severity of the cirrhosis [69, 71–73] although not all investigators have consistently observed this pattern [75]. Multiple mechanisms are implicated in the generation and maintenance

of hyperventilation-induced respiratory alkalosis in these patients. Patients with cirrhosis have elevated circulating of progestins [72, 75], a direct stimulant to central breathing centers, and estrogens, which can potentiate progesterone's effects [75]. With increasing severity of cirrhosis, patients also become less tolerant to hypercapnia, a concept called the central chemosensitivity [71]. Chemosensitization is not only linked to Childs-Pugh class of cirrhosis but also to circulating progestins and norepinephrine [71]. In patients with Childs-Pugh class A cirrhosis, hyperventilation appears to be primarily a consequence of increased tidal volumes [71]. With progressive severity of cirrhosis, patients also develop a moderate degree of tachypnea, further alkalinizing the blood and driving down arterial  $P_{CO_2}$  [71]. The degree of hyperventilation also correlates with measurements of a hyperdynamic circulation such as an increased cardiac index and decreased systemic vascular resistance [71]. Thus, changes in ventilatory patterns may reflect influences from the sympathetic nervous system and incompletely understood circulatory-pulmonary interactions. Interestingly, despite often marked hyperventilation and hypocapnia, the acid-base status of the serum remains relatively neutral owing to counterbalancing influences of hypoalbuminemia and hemodilution [71, 73]. That primary respiratory alkalosis resolves after liver transplantation [8] affirms that the milieu of liver disease indeed is causative.

### 3.6 Diffusion of Oxygen and Abnormalities in Diffusion Capacity

The most consistent abnormality in pulmonary function tests in patients with chronic liver disease is an abnormally decreased diffusion capacity of carbon monoxide (DLCO). [8, 28, 35] Decrements in DLCO are typical of restrictive lung disease, but reduced DLCO often occurs in cirrhotic patients even in the absence of a restrictive defect [28]. Like other pulmonary manifestations of liver disease, decrements in DLCO are related to the severity of the underlying liver disorder [13, 76]. Abnormally low DLCO's are characteristic of the hepatopulmonary syndrome (HPS) [77], but clinically relevant changes in DLCO are observed even in the absence of the characteristic intrapulmonary shunting of HPS [28, 58, 78]. That said, once a patient has developed intrapulmonary shunting, the shunt becomes the dominant mechanism of hypoxemia and reduced DLCO, overriding the effects of underlying cardiopulmonary disease [79]. Intrapulmonary shunting can develop as a chronic complication of longstanding liver disease or acutely, such as in the context of acute ischemic hepatitis [80].

A detailed review of HPS is found in Chapter 11, so we will focus on reviewing the mechanisms of reduced DLCO

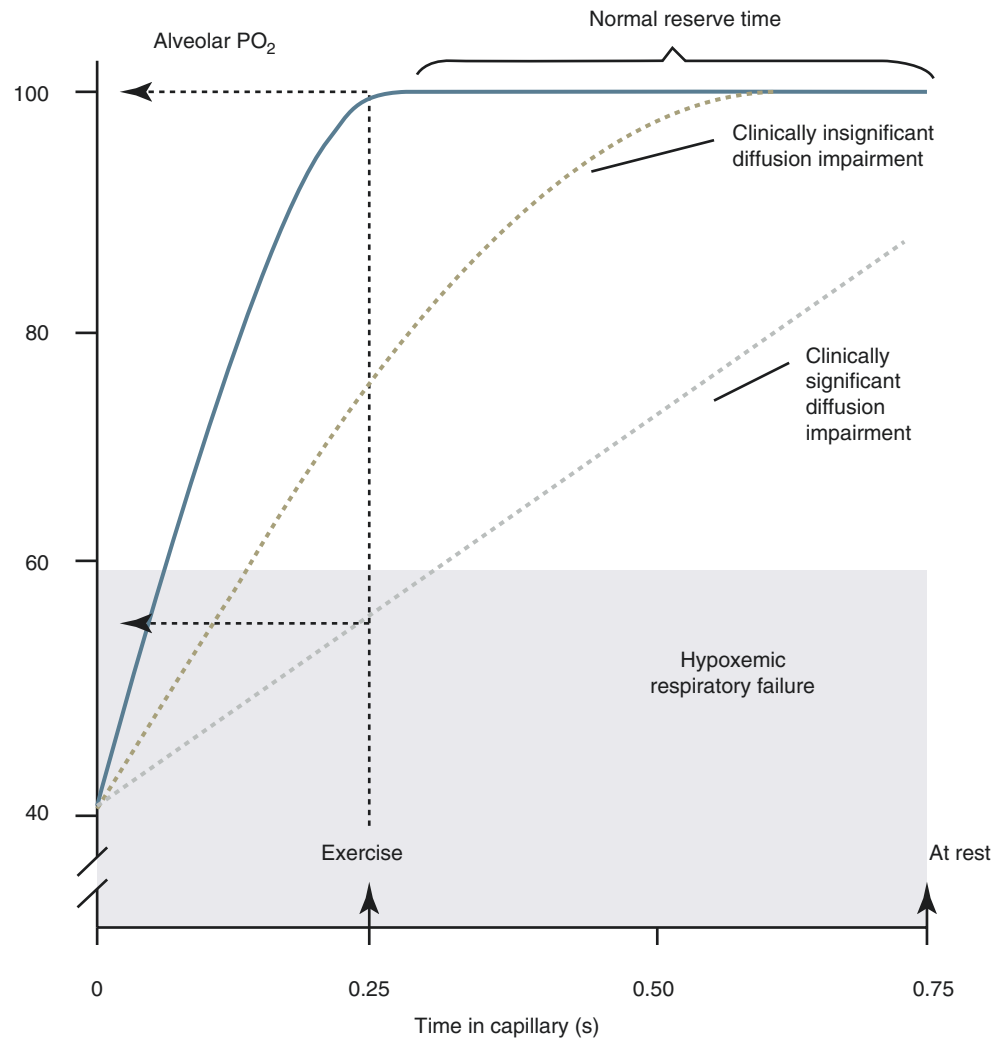
in patients without significant intrapulmonary shunt, almost all of whom do not exhibit significant arterial hypoxemia [28]. Recall that DLCO is nearly always measured by the single breath carbon monoxide test, and the results provide a very practical assessment of the ability of the lungs to transfer gas from the mouth into the alveoli and subsequently into the pulmonary capillary bed. However, several factors can alter DLCO that do not necessarily reflect a disorder of diffusion at the level of the alveolus-capillary interface. These include the effects of lung volumes, dynamic small airway closure, and the volume and distribution of capillary blood. DLCO is also influenced by hemoglobin concentration and the presence of interstitial edema [1, 4, 81]. In evaluating patients with liver disease with an abnormal DLCO, these factors may all be perturbed: patients with liver disease are prone to reduced lung volumes, dynamic airway closure, anasarca, and anemia. In fact, much of the perceived difference between DLCO in cirrhotic patients and healthy controls may be attributable to these factors. Furthermore, a reduced DLCO may reflect findings from a concomitant disorder such as emphysematous COPD or interstitial lung disease, both of which may occur with increased frequency in patients with chronic liver disease.

In the normal physiologic state of healthy subjects, oxygen diffuses into pulmonary capillaries and maximally saturates hemoglobin within the first third of the cardiac cycle (as represented by the normal reserve time in Fig. 3.5). Not surprisingly, patients with cirrhosis who have a normal DLCO and are normoxemic at baseline do not exhibit significant diffusion block (as measured by V-Q matching) during metabolic stress like exercise [82]. Because diffusion of oxygen into pulmonary capillaries is a time-dependent process, increases in heart rate can worsen arterial hypoxemia in patients with clinically significant diffusion blocks at baseline. Indeed cirrhotic patients with clinically apparent arterial hypoxemia, widened A-a gradient, and reduced DLCO at baseline have a pathologically widening A-a gradient during exercise [78]. Whether these data are transferrable to the critical care setting are not known, but presumably the cardiopulmonary response of exercise mimics many of the distributive shock states seen in critical illness.

### 3.7 V-Q Matching [83]

V-Q matching is clinically more relevant in the pathophysiology of arterial hypoxemia, and a detailed overview of hypoxemia in liver disease is beyond the scope of this chapter. (Readers are directed to the excellent discussion in the following chapter). However, we will briefly review the normal physiology of V-Q matching and highlight specific clinical scenarios in liver disease in which V-Q mismatching occurs.

**Fig. 3.5** Relationship between alveolar partial pressures of oxygen and the time spent by blood in the pulmonary capillaries. From *Murray & Nadel's Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. (Figure 4-17). Reprinted with permission from the publisher

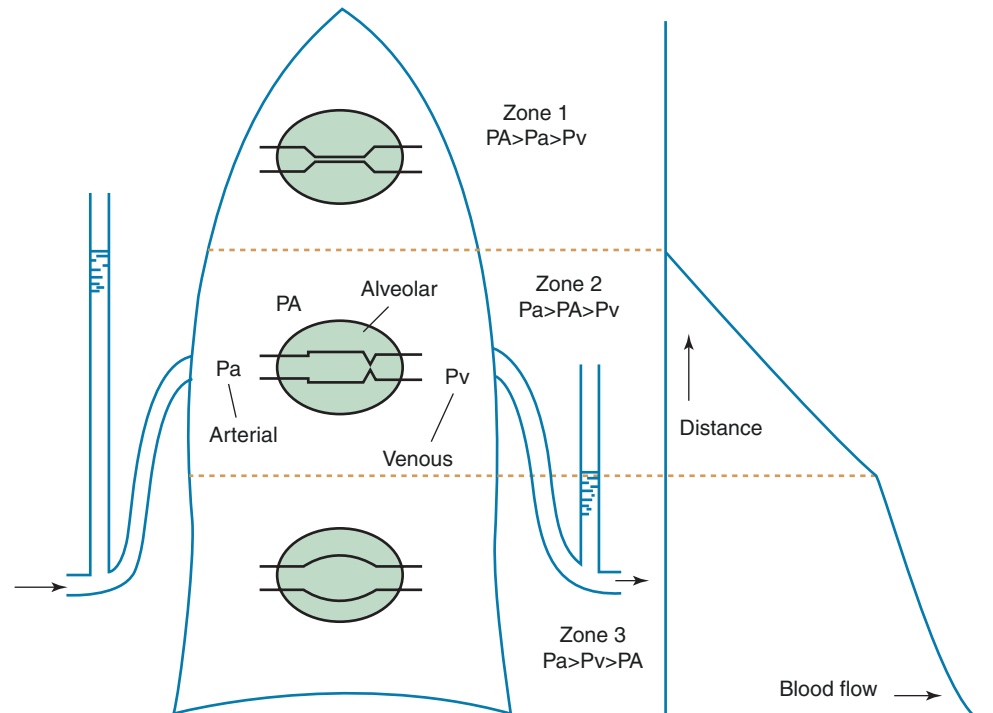


Recall that both ventilation and perfusion have variable regional distributions in the lung. The uneven distribution of ventilation and blood flow are predominantly attributable to the differential effects of gravity in the regions of the lung. In upright healthy subjects, ventilation per unit of alveolar volume progressively increases from the apex down to the basilar regions of the lung. When patients are supine or prone, ventilation and pulmonary blood flow are still preferentially distributed to more dependent regions. Nongravitational factors also affect the distribution of ventilation and include the variable flows and time-constants of alveoli in different regions of the lungs. Ultimately, the differential distribution of alveolar ventilation and capillary blood flow can be simplified into a three-zone model (commonly called West zones) as seen in Fig. 3.6. In zone 1, alveolar pressure ( $P_A$ ) exceeds both arterial and venous pressures, thus making blood flow in this zone virtually zero. In zone 2, the pulmonary arteriolar pressure ( $P_a$ ) exceeds  $P_A$ , and pulmonary blood flow is determined by the resistance of alveolar pressure. Finally in zone 3, pulmonary blood flow is not depen-

dent on external alveolar pressures because venous pressure ( $P_v$ ) exceeds  $P_A$ . In this model, it is not surprising that the most dependent region (West zone 3) contributes most significantly to gas exchange and V-Q matching. Recall that the pulmonary circulation is also actively regulated with hypoxic pulmonary vasoconstriction representing the best known and understood mechanism by which ventilation and perfusion are matched.

In health, the ventilation and perfusion for the entire lung are perfectly balanced albeit unevenly distributed as discussed above. Any disorder that affects either ventilation or perfusion will create mismatch and thus will lead to suboptimal gas exchange. In patients with liver disease, several processes may contribute to V-Q mismatching including atelectasis from ascites or pleural effusions [19, 45, 49], imbalanced matching in hepatopulmonary syndrome from intrapulmonary shunting and poor diffusion [77], or dynamic small airway collapse from increased pulmonary blood flow [32, 35]. All of these disorders tend to affect lung in West zone 3; thus V-Q mismatching in these basilar regions results

**Fig. 3.6** The three-zone model of distribution of ventilation and pulmonary blood flow. See text for details. From Murray & Nadel's *Textbook of Respiratory Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. (Figure 4-11). Reprinted with permission from the publisher



in even more significant hypoxemia. V-Q mismatching is also caused by various other disorders that may affect patients with liver disease more frequently, including aspiration pneumonitis related to encephalopathy, bacterial pneumonia from the immunocompromising state of cirrhosis, and atelectasis and mucous plugging due to poor inspiratory and expiratory muscle strength.

### 3.8 Integration of Concepts: A Case Study in ARDS

To conclude our discussion, we will integrate and expand on the concepts of respiratory physiology in liver disease in the context of a condition intensivists regularly encounter: ARDS.

A 53 year-old man with a history of Childs-Pugh class C alcoholic cirrhosis is brought to the emergency department after being found lying in a soiled bed by his son. Several empty bottles of hard liquor were found at the scene, and the patient was last seen behaving normally three days ago. On presentation, he is tachypneic with a respiratory rate of 32 and has a resting pulse oximetry of 74% on room air. Even with 15 L of supplemental oxygen by face mask, he is unable to achieve an oxygen saturation above 87% by oximetry. He is cachectic with obvious jaundice and tense ascites on abdominal examination. His Glasgow coma score is 7, and he is minimally arousable to sternal rub. A portable chest radiograph reveals bilateral interstitial and alveolar infiltrates and a large right-sided pleural effusion. A stat head

CT reveals evidence of mild cerebral edema. Laboratory studies are remarkable for an INR of 6.7 and total bilirubin of 28 mg/dL.

The patient is promptly intubated in the emergency department for hypoxemia and inadequate airway protection. He is placed on 100% FiO<sub>2</sub> and 18 cm H<sub>2</sub>O of PEEP with initial ventilator settings also including a tidal volume of 6 mL/kg of ideal body weight. An arterial blood gas 1 h later reveals pH of 7.52, P<sub>CO</sub><sub>2</sub> of 24 mmHg, and PaO<sub>2</sub> of 51 mmHg. The patient is transferred to the intensive care unit with a presumptive diagnosis of acute on chronic liver failure and ARDS secondary to aspiration pneumonitis.

Despite continuous infusions of propofol and fentanyl, the patient continues to overbreathe the vent and is exhibiting significant dyssynchrony. Plateau pressures are 43 cm H<sub>2</sub>O, and the patient's saturation by pulse oximetry is only 86%.

How should this patient with ARDS and concomitant advanced liver disease be managed?

Most intensivists are likely familiar with treatments that have been proven to reduce the mortality associated with ARDS: specifically, lung protective ventilation with a low tidal volume strategy [84], early neuromuscular blockade in patients with moderate ARDS [85], and prone positioning in patients with severe ARDS [86]. Unfortunately, there have been no prospective trials comparing optimal ventilation strategy in patients with liver disease who suffer acute respiratory failure or ARDS. In fact, landmark trials such as the original ARDSNet trial and ACURASYS study of neuromuscular blockade excluded patients with advanced cirrhosis as defined by Childs-Pugh class C [85, 87], and the



pinnacle PROSEVA trial that established proning as a life-saving strategy excluded patients with elevated intracranial pressure [84], a finding commonly seen in acute liver failure. Thus, optimal ventilator management of ARDS in patients with acute or advanced chronic liver disease requires consideration of the pathophysiology of liver disease itself and its myriad effects on pulmonary physiology and extra-pulmonary organs.

Lung-protective ventilation involves the use of low tidal volumes, and many intensivists may routinely use other aspects of the Acute Respiratory Distress Syndrome Network (ARDSNet) protocol deliberately or subconsciously such as targeted plateau pressures, high PEEP, and permissive hypercapnia. All of these aspects of managing ARDS require special consideration in patients with liver disease. The targeted plateau pressure per the ARDSNet protocol was 30 cm H<sub>2</sub>O with the goal of minimizing excessive lung stretch. Most critical care practitioners will recognize that plateau pressures in fact reflect the entirety of the respiratory system's compliance, not simply lung compliance. Very elevated plateau pressures in patients with liver disease, such as seen in our example case, may be a consequence from the combination of lung water and intra-abdominal hypertension from tense ascites. As such, in our example case, every effort should be made to improve both lung compliance and respiratory system compliance by draining tense ascites and hepatic hydrothorax (when safely feasible) and maintaining a conservative approach toward fluid replacement to minimize lung water. The ARDSNet protocol also allowed PEEP up to 18–24 cm H<sub>2</sub>O in patients receiving an FiO<sub>2</sub> of 100%. While high PEEP may be necessary to recruit partially consolidated lung and to improve oxygenation, this level of PEEP can have at least two potential deleterious effects on patients like our test case. First, the degree to which PEEP is transmitted to the cerebral venous pressure is not firmly established with investigators reporting various effects in ventilated patients [88–90]. It may be prudent to avoid very high PEEP in patients who have evidence of elevated intracranial pressure, such as in our case. In addition, high PEEP can potentially impair hepato-splanchnic circulation [91, 92], and these concerns may be particularly relevant in patients with intra-abdominal hypertension from ascites. Finally, with permissive hypercapnia, clinicians may allow an iatrogenic respiratory acidosis to ensue. However, in patients who are at risk for cerebral edema, such as the gentleman in our case, this rise in pCO<sub>2</sub> may be accompanied by the unwanted effects of raising intracranial pressure.

Neuromuscular blockade is a potential option for managing refractory hypoxemia in ARDS, and its benefit has been established in patients with moderate ARDS. The exact mechanism by which neuromuscular blockade improves outcomes is unclear; the salutary effects of neuromuscular

blockade do not appear to be mediated by improvements in respiratory system compliance or levels of PEEP required [85]. In our example case, cisatracurium may have a role in improving ventilator synchrony; the combination of sedation, a respiratory depressant, and a neuromuscular blocker may be required to override the patient's inherent tendency to hyperventilate. Overall, cisatracurium appears to be safe even in end-stage liver disease [93], but recall that patients with advanced cirrhosis were excluded from the landmark ACURASYS trial [85].

Proning has a predictable effect of improving gas exchange and oxygenation in ARDS, predominantly by improving ventilation to dorsal lung regions and reducing pleural pressure gradients [94]. The decision to prone patients like the gentleman in our case requires a careful consideration of potential benefits against the obvious downsides. On the one hand, animal models have demonstrated that proning improves gas exchange even more markedly when concomitant intra-abdominal hypertension or volume overload are present [95, 96]. Thus if draining our patient's ascites did not substantially improve gas exchange and respiratory mechanics, then proning may provide additional benefit. Furthermore, while proning is expected to reduce chest wall compliance, it may be accompanied by an overall improvement in respiratory system compliance, presumably due to improvement recruitment of previously collapsed dorsal lung regions [97]. Unfortunately, proning could be logistically difficult in patients with rapidly reaccumulating ascites, and it would be potentially dangerous in patients with elevated intracranial pressure (ICP) from cerebral edema. Due to concerns about altering ICP, patients with ICP >30 mmHg or cerebral perfusion pressure <60 mmHg have been excluded from the most important proning trials [86]. In addition, proning can also have deleterious effects on intra-abdominal organ perfusion when intra-abdominal hypertension is already present [92].

In summary, clinicians managing patients with liver failure complicated by ARDS should likely use well established treatment strategies for ARDS and should focus on modifiable aspects of respiratory system physiology in liver disease, such as ascites. Because paracentesis improves respiratory system compliance and oxygenation, it should generally be performed in these settings if feasible. Clinicians should have a command of the other physiologic perturbations of the respiratory system that are common in liver disease but must also recognize that many of these abnormalities are not readily remedied at the bedside. Furthermore, accepted strategies used to support patients through the severe physiologic stresses of ARDS can have extrapulmonary consequences in patients with liver failure, and inclinations to manipulate the physiology of the respiratory system must be weighed against these consequences.



### 3.9 Questions for Review

A 44 year-old woman with autoimmune hepatitis complicated by Childs-Pugh class B cirrhosis is being evaluated for liver transplantation and undergoes routine pulmonary function tests. She has a history of refractory ascites and chronic subacute gastrointestinal blood loss from portal gastropathy. She has been a lifelong non-smoker and denies any history of cardiac or pulmonary disease. She experiences dyspnea with moderately intense exercise.

Which of the following findings is most likely to be seen on her pulmonary function tests?

- A. Reduced forced expiratory volume in 1 s (FEV1)
- B. Abnormally high total lung capacity (TLC)
- C. Abnormally high forced vital capacity (FVC)
- D. Abnormally reduced diffusion capacity (DLCO)
- E. Increased functional residual capacity (FRC)

*Answer: D—Abnormally reduced diffusion capacity*

*Recall that low DLCO is the most common abnormality seen on PFT's in patients with chronic liver disease. Reductions in DLCO in these populations often reflect the presence of small airway closure or mildly reduced lung volumes and may be in part artefactual due to concomitant anemia.*

*Reductions in FEV1 are not an expected consequence of cirrhosis, and patients with cirrhosis do not appear to have an appreciably increased risk of obstructive lung disease. TLC, FVC, and FRC are all commonly decreased in the face of chronic liver disease.*

A 61 year-old man with a history of hepatitis C-associated cirrhosis is hospitalized with community acquired pneumonia complicated by ARDS. He has been intubated for 8 days, and he is to undergo a spontaneous breathing trial to assess readiness for extubation. On examination today, he is found to have moderate ascites by percussion and bedside ultrasonography. Which of the following mechanisms best explains why the drainage of ascites will facilitate successful extubation?

- A. Relieving ascites increases intrinsic PEEP.
- B. Lung elastance improves with reductions in intra-abdominal hydrostatic pressure.
- C. Trans-diaphragmatic pressure swings decrease after the drainage of ascites, thereby reducing work of breathing.
- D. Draining ascites significantly improves inspiratory muscle strength.

*Answer: C—Work of breathing is reduced.*

*When intra-abdominal hydrostatic pressure is elevated, more dramatic swings in trans-diaphragmatic pressure are required to adequately ventilate. Alleviating this intra-*

*abdominal pressure reduces said pressure swings and accordingly improves work of breathing—and not surprisingly, dyspnea. Relieving ascites also improves mechanics by reducing intrinsic PEEP and improving lung compliance (not elastance). As noted in the chapter, the removal of ascites does not appear to affect inspiratory muscle strength.*

### References

1. Lumb AB, Nunn JF. Nunn's applied respiratory physiology. 8th ed. Edinburgh: Churchill Livingstone, Elsevier; 2017:1 online resource (xii, 556 pages): illustrations (some color). 123Library [http://www.123library.org/book\\_details/?id=46803](http://www.123library.org/book_details/?id=46803); ClinicalKey <http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C2009055355X>; ClinicalKey <http://www.clinicalkey.com.au/dura/browse/bookChapter/3-s2.0-C2009055355X>; ebrary <http://site.ebrary.com/id/10537298>; EBSCOhost <http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=973648>.
2. Grinnan DC, Truwit JD. Clinical review: respiratory mechanics in spontaneous and assisted ventilation. Crit Care. 2005;9(5):472–84.
3. Slonim NB, Hamilton LH. Respiratory physiology. 5th ed. St. Louis, MI: The C.V. Mosby Company; 1987.
4. West JB. Pulmonary pathophysiology: The essentials. 8th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2013.
5. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511–22.
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948–68.
7. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest. 1999;115(3):869–73.
8. Krowka MJ, Dickson ER, Wiesner RH, Krom RA, Atkinson B, Cortese DA. A prospective study of pulmonary function and gas exchange following liver transplantation. Chest. 1992;102(4):1161–6.
9. Yao EH, Kong BC, Hsue GL, Zhou AC, Wang H. Pulmonary function changes in cirrhosis of the liver. Am J Gastroenterol. 1987;82(4):352–4.
10. Nagral A, Kolhatkar VP, Bhatia SJ, Taskar VS, Abraham P. Pulmonary function tests in cirrhotic and non-cirrhotic portal hypertension. Indian J Gastroenterol. 1993;12(2):36–40.
11. Abelman WH, Frank NR, Gaensler EA, Cugell DW. Effects of abdominal distention by ascites on lung volumes and ventilation. AMA Arch Intern Med. 1954;93(4):528–40.
12. Hanson CA, Ritter AB, Duran W, Lavietes MH. Ascites: its effect upon static inflation of the respiratory system. Am Rev Respir Dis. 1990;142(1):39–42.
13. Yigit IP, Hacıevliyagil SS, Seckin Y, Oner RI, Karıncaoglu M. The relationship between severity of liver cirrhosis and pulmonary function tests. Dig Dis Sci. 2008;53(7):1951–6.
14. Levesque E, Hoti E, Azoulay D, et al. Pulmonary complications after elective liver transplantation—incidence, risk factors, and outcome. Transplantation. 2012;94(5):532–8.
15. Mutoh T, Lamm WJ, Embree LJ, Hildebrandt J, Albert RK. Volume infusion produces abdominal distension, lung compression, and chest wall stiffening in pigs. J Appl Physiol (1985). 1992;72(2):575–82.
16. Berkowitz KA, Butensky MS, Smith RL. Pulmonary function changes after large volume paracentesis. Am J Gastroenterol. 1993;88(6):905–7.

17. Angueira CE, Kadakia SC. Effects of large-volume paracentesis on pulmonary function in patients with tense cirrhotic ascites. *Hepatology*. 1994;20(4 Pt 1):825–8.
18. Chao Y, Wang SS, Lee SD, Shiao GM, Chang HI, Chang SC. Effect of large-volume paracentesis on pulmonary function in patients with cirrhosis and tense ascites. *J Hepatol*. 1994;20(1):101–5.
19. Chang SC, Chang HI, Chen FJ, Shiao GM, Wang SS, Lee SD. Therapeutic effects of diuretics and paracentesis on lung function in patients with non-alcoholic cirrhosis and tense ascites. *J Hepatol*. 1997;26(4):833–8.
20. Levesque E, Hoti E, Jiabin J, et al. Respiratory impact of paracentesis in cirrhotic patients with acute lung injury. *J Crit Care*. 2011;26(3):257–61.
21. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: A modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesth Analg*. 2005;101(1):206–12. table of contents
22. Peng TC, Kao TW, Wu LW, et al. Association between pulmonary function and nonalcoholic fatty liver disease in the NHANES III study. *Medicine (Baltimore)*. 2015;94(21):e907.
23. Jung DH, Shim JY, Lee HR, Moon BS, Park BJ, Lee YJ. Relationship between non-alcoholic fatty liver disease and pulmonary function. *Intern Med J*. 2012;42(5):541–6.
24. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med*. 2009;179(6):509–16.
25. Ford ES, Mannino DM, Health N, Study NESE F-u. Prospective association between lung function and the incidence of diabetes: findings from the national health and nutrition examination survey epidemiologic follow-up study. *Diabetes Care*. 2004;27(12):2966–70.
26. Aronson D, Roterman I, Yigla M, et al. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. *Am J Respir Crit Care Med*. 2006;174(6):626–32.
27. Park MS, Lee MH, Park YS, Kim SH, Kwak MJ, Kang JS. Abnormal gas diffusing capacity and portosystemic shunt in patients with chronic liver disease. *Gastroenterol Res*. 2012;5(5):182–9.
28. Hourani JM, Bellamy PE, Tashkin DP, Batra P, Simmons MS. Pulmonary dysfunction in advanced liver disease: frequent occurrence of an abnormal diffusing capacity. *Am J Med*. 1991;90(6):693–700.
29. Godfrey MS, Jankowich MD. The vital capacity is vital: epidemiology and clinical significance of the restrictive spirometry pattern. *Chest*. 2016;149(1):238–51.
30. Miller MR, Sokol RJ, Narkewicz MR, Sontag MK. Pulmonary function in individuals who underwent liver transplantation: from the US cystic fibrosis foundation registry. *Liver Transpl*. 2012;18(5):585–93.
31. Carey EJ, Iyer VN, Nelson DR, Nguyen JH, Krowka MJ. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency-related cirrhosis. *Liver Transpl*. 2013;19(12):1370–6.
32. Furukawa T, Hara N, Yasumoto K, Inokuchi K. Arterial hypoxemia in patients with hepatic cirrhosis. *Am J Med Sci*. 1984;287(3):10–3.
33. Caruso G, Catalano D, Corsaro A, et al. Respiratory function and liver cirrhosis. *Riv Eur Sci Med Farmacol*. 1990;12(2):83–9.
34. Domino KB, Eisenstein BL, Tran T, Hlastala MP. Increased pulmonary perfusion worsens ventilation-perfusion matching. *Anesthesiology*. 1993;79(4):817–26.
35. Ruff F, Hughes JM, Stanley N, et al. Regional lung function in patients with hepatic cirrhosis. *J Clin Invest*. 1971;50(11):2403–13.
36. Funahashi A, Kutty AV, Prater SL. Hypoxaemia and cirrhosis of the liver. *Thorax*. 1976;31(3):303–8.
37. Hara N, Yoshida T, Furukawa T, Inokuchi K. Abnormalities in maximum flow volume curve and closing volume in patients with hepatic cirrhosis. *Jpn J Surg*. 1980;10(4):265–9.
38. Burgel PR. The role of small airways in obstructive airway diseases. *Eur Respir Rev*. 2011;20(119):23–33.
39. Braidó F, Scichilone N, Lavorini F, et al. Manifesto on small airway involvement and management in asthma and chronic obstructive pulmonary disease: an interasma (global asthma association—GAA) and world allergy organization (WAO) document endorsed by allergic rhinitis and its impact on asthma (ARIA) and global allergy and asthma European network (GA2LEN). *Asthma Res Pract*. 2016;2:12.
40. Usmani OS. Small-airway disease in asthma: Pharmacological considerations. *Curr Opin Pulm Med*. 2015;21(1):55–67.
41. Burgel PR, Bergeron A, de Blic J, et al. Small airways diseases, excluding asthma and COPD: an overview. *Eur Respir Rev*. 2013;22(128):131–47.
42. Hayes D Jr, Kraman SS. The physiologic basis of spirometry. *Respir Care*. 2009;54(12):1717–26.
43. Pride NB, Permutt S, Riley RL, Bromberger-Barnea B. Determinants of maximal expiratory flow from the lungs. *J Appl Physiol*. 1967;23(5):646–62.
44. Cullen DJ, Coyle JP, Teplick R, Long MC. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. *Crit Care Med*. 1989;17(2):118–21.
45. Mutoh T, Lamm WJ, Embree LJ, Hildebrandt J, Albert RK. Abdominal distension alters regional pleural pressures and chest wall mechanics in pigs in vivo. *J Appl Physiol* (1985). 1991;70(6):2611–8.
46. Wauters J, Claus P, Brosens N, et al. Relationship between abdominal pressure, pulmonary compliance, and cardiac preload in a porcine model. *Crit Care Res Pract*. 2012;2012:763181.
47. Duranti R, Laffi G, Misuri G, et al. Respiratory mechanics in patients with tense cirrhotic ascites. *Eur Respir J*. 1997;10(7):1622–30.
48. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol* (1985). 1988;65(4):1488–99.
49. Phillip V, Saugel B, Ernesti C, et al. Effects of paracentesis on hemodynamic parameters and respiratory function in critically ill patients. *BMC Gastroenterol*. 2014;14:18. <https://doi.org/10.1186/1471-230X-14-18>.
50. Lazaridis KN, Frank JW, Krowka MJ, Kamath PS. Hepatic hydrothorax: pathogenesis, diagnosis, and management. *Am J Med*. 1999;107(3):262–7.
51. Malagari K, Nikita A, Alexopoulou E, et al. Cirrhosis-related intrathoracic disease. imaging features in 1038 patients. *Hepato-Gastroenterology*. 2005;52(62):558–62.
52. Furukawa T, Yasumoto K, Inokuchi K. Pulmonary interstitial edema in experimental cirrhosis of the liver in rats. *Eur Surg Res*. 1984;16(6):366–71.
53. Hauge A, Bo G, Waaler BA. Interrelations between pulmonary liquid volumes and lung compliance. *J Appl Physiol*. 1975;38(4):608–14.
54. Noble WH, Kay JC, Obdrzalek J. Lung mechanics in hypervolemic pulmonary edema. *J Appl Physiol*. 1975;38(4):681–7.
55. Fritz JS, Fallon MB, Kawut SM. Pulmonary vascular complications of liver disease. *Am J Respir Crit Care Med*. 2013;187(2):133–43.
56. Khan AN, Al-Jahdali H, Abdullah K, Irion KL, Sabih Q, Gouda A. Pulmonary vascular complications of chronic liver disease: pathophysiology, imaging, and treatment. *Ann Thorac Med*. 2011;6(2):57–65.
57. Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. *Respir Care*. 2009;54(10):1348–59.
58. Terziyski K, Andonov V, Marinov B, Kostianev S. Exercise performance and ventilatory efficiency in patients with mild and moderate liver cirrhosis. *Clin Exp Pharmacol Physiol*. 2008;35(2):135–40.
59. Kaltsakas G, Antoniou E, Palamidis AF, et al. Dyspnea and respiratory muscle strength in end-stage liver disease. *World J Hepatol*. 2013;5(2):56–63.

60. Augusto VS, Castro E, Silva O, Souza ME, Sankarankutty AK. Evaluation of the respiratory muscle strength of cirrhotic patients: relationship with child-turcotte-pugh scoring system. *Transplant Proc.* 2008;40(3):774–6.
61. Galant LH, Ferrari R, Forgiarini LA Jr, Monteiro MB, Marroni CA, Dias AS. Relationship between MELD severity score and the distance walked and respiratory muscle strength in candidates for liver transplantation. *Transplant Proc.* 2010;42(5):1729–30.
62. da Silva AM, Cliquet A Jr, Boin IF. Profile of respiratory evaluation through surface electromyography, manovacuometry, and spirometry in candidates on the liver transplant waiting list. *Transplant Proc.* 2012;44(8):2403–5.
63. Carlucci A, Ceriana P, Prinianakis G, Fanfulla F, Colombo R, Nava S. Determinants of weaning success in patients with prolonged mechanical ventilation. *Crit Care.* 2009;13(3):R97.
64. Martin AD, Smith BK, Davenport PD, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: A randomized trial. *Crit Care.* 2011;15(2):R84.
65. Vallverdu I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1998;158(6):1855–62.
66. Faustini Pereira JL, Galant LH, Rossi D, et al. Functional capacity, respiratory muscle strength, and oxygen consumption predict mortality in patients with cirrhosis. *Can J Gastroenterol Hepatol.* 2016;2016:6940374.
67. Spyer KM, Gourine AV. Chemosensory pathways in the brainstem controlling cardiorespiratory activity. *Philos Trans R Soc Lond Ser B Biol Sci.* 2009;364(1529):2603–10.
68. HEINEMANN HO, EMIRGIL C, MIJNSEN JP. Hyperventilation and arterial hypoxemia in cirrhosis of the liver. *Am J Med.* 1960;28:239–46.
69. Moreau R, Hadengue A, Soupison T, et al. Arterial and mixed venous acid-base status in patients with cirrhosis. influence of liver failure. *Liver.* 1993;13(1):20–4.
70. Oster JR, Perez GO. Acid-base disturbances in liver disease. *J Hepatol.* 1986;2(2):299–306.
71. Henriksen JH, Bendtsen F, Moller S. Acid-base disturbance in patients with cirrhosis: relation to hemodynamic dysfunction. *Eur J Gastroenterol Hepatol.* 2015;27(8):920–7.
72. Passino C, Giannoni A, Mannucci F, et al. Abnormal hyperventilation in patients with hepatic cirrhosis: role of enhanced chemosensitivity to carbon dioxide. *Int J Cardiol.* 2012;154(1):22–6.
73. Funk GC, Doberer D, Osterreicher C, Peck-Radosavljevic M, Schmid M, Schneeweiss B. Equilibrium of acidifying and alkalizing metabolic acid-base disorders in cirrhosis. *Liver Int.* 2005;25(3):505–12.
74. Record CO, Iles RA, Cohen RD, Williams R. Acid-base and metabolic disturbances in fulminant hepatic failure. *Gut.* 1975;16(2):144–9.
75. Lustik SJ, Chhibber AK, Kolano JW, et al. The hyperventilation of cirrhosis: progesterone and estradiol effects. *Hepatology.* 1997;25(1):55–8.
76. Huo YM, Hua R, Chen W, Sun YW. Clinical study on pulmonary diffusion function in patients with chronic liver disease. *J Dig Dis.* 2010;11(5):291–8.
77. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome—a liver-induced lung vascular disorder. *N Engl J Med.* 2008;358(22):2378–87.
78. Lemyze M, Dharancy S, Neviere R, Wallaert B. Cardiopulmonary response to exercise in patients with liver cirrhosis and impaired pulmonary gas exchange. *Respir Med.* 2011;105(10):1550–6.
79. Martinez G, Barbera JA, Navasa M, Roca J, Visa J, Rodriguez-Roisin R. Hepatopulmonary syndrome associated with cardiorespiratory disease. *J Hepatol.* 1999;30(5):882–9.
80. Fuhrmann V, Madl C, Mueller C, et al. Hepatopulmonary syndrome in patients with hypoxic hepatitis. *Gastroenterology.* 2006;131(1):69–75.
81. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J.* 2005;26(4):720–35.
82. Agusti AG, Roca J, Rodriguez-Roisin R, Mastai R, Wagner PD, Bosch J. Pulmonary hemodynamics and gas exchange during exercise in liver cirrhosis. *Am Rev Respir Dis.* 1989;139(2):485–91.
83. Powell F, Wagner P, West J. Ventilation, blood flow, and gas exchange. In: Broaddus VC, Mason RJ, Ernst J, King T, et al., editors. *Murray & Nadel's textbook of respiratory medicine.* 6th ed. Philadelphia, PA: Elsevier Saunders; 2016. p. 44–75.
84. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev.* 2013;(2):CD003844. doi:10.1002/14651858.CD003844.pub4.
85. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363(12):1107–16.
86. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013;368(23):2159–68.
87. The Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301–8.
88. Caricato A, Conti G, Della Corte F, et al. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: The role of respiratory system compliance. *J Trauma.* 2005;58(3):571–6.
89. Frost EA. Effects of positive end-expiratory pressure on intracranial pressure and compliance in brain-injured patients. *J Neurosurg.* 1977;47(2):195–200.
90. Videtta W, Villarejo F, Cohen M, et al. Effects of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Acta Neurochir Suppl.* 2002;81:93–7.
91. Jakob SM. The effects of mechanical ventilation on hepatosplanchnic perfusion. *Curr Opin Crit Care.* 2010;16(2):165–8.
92. Putensen C, Wrigge H, Hering R. The effects of mechanical ventilation on the gut and abdomen. *Curr Opin Crit Care.* 2006;12(2):160–5.
93. De Wolf AM, Freeman JA, Scott VL, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. *Br J Anaesth.* 1996;76(5):624–8.
94. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS with prone positioning. *Chest.* 2017;151(1):215–24.
95. Mure M, Glenny RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med.* 1998;157(6 Pt 1):1785–90.
96. Mutoh T, Guest RJ, Lamm WJ, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. *Am Rev Respir Dis.* 1992;146(2):300–6.
97. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med.* 1998;157(2):387–93.

J.P. Norvell, Anjana A. Pillai, and Mary M. Flynn

## Abstract

Portal hypertension develops as a consequence of increased resistance to portal blood flow as well as increased portal blood flow due to splanchnic vasodilation. Increased resistance due to cirrhosis is due to both structural changes from increased vascular resistance as well as dynamic variables due to release of endothelial vasodilators (such as nitrous oxide) and increased production of vasoconstrictors (such as endothelin 1). While portal hypertension is initially asymptomatic, its development is a necessary precursor for many of the potentially lethal complications related to liver disease. Portosystemic collateral vessels, or varices, develop as an inefficient means to decompress the portal system and can result in esophageal or gastric hemorrhage associated with high morbidity and mortality. A compensatory activation of neurohormonal mechanism to reduced effective circulating volume leads to sodium and water retention results in ascites and eventually to hepatorenal syndrome. Acute liver failure is characterized as the acute development of liver injury, hepatic encephalopathy, and impaired synthetic dysfunction and leads to hemodynamic instability and multi-organ system failure. Acute on chronic liver failure is a recently defined syndrome characterized by hemodynamic abnormalities with complications resulting from portal hypertension.

## Keywords

Portal hypertension • Acute liver failure • Acute on chronic liver failure • Nitric oxide  
Hyperdynamic circulation • Varices • Ascites • Spontaneous bacterial peritonitis • Renal  
vasoconstriction • Hepatorenal syndrome

J.P. Norvell, M.D. (✉)

Assitant Professor of Medicine, Division of Gastroenterology and Hepatology, University of Colorado, Anschutz Medical Campus, 1635 Aurora Ct./Mail Stop B154, Aurora, CO 80045, USA  
e-mail: [john.norvell@ucdenver.edu](mailto:john.norvell@ucdenver.edu)

A.A. Pillai, M.D.

Associate Professor of Medicine, The University of Chicago Medical Center and Biological Sciences, 5841 S. Maryland Ave/MC 7120, Chicago, IL 60637, USA  
e-mail: [apillai1@medicine.bsd.uchicago.edu](mailto:apillai1@medicine.bsd.uchicago.edu)

M.M. Flynn, M.D.

Gastroenterology Fellow, Division of Digestive Diseases, Emory University School of Medicine, 1365 Clifton Rd, Suite B6100, Atlanta, GA 30322, USA  
e-mail: [mary.margaret.flynn@emory.edu](mailto:mary.margaret.flynn@emory.edu)

## Learning Objectives

- Understand definition and hemodynamic changes in acute liver failure and acute on chronic liver failure syndromes.
- Understand the definition and mechanisms for development of portal hypertension including changes in the responsible vasodilators and vasoconstrictors.
- Understand the mechanism leading to the complications of portal hypertension, including gastroesophageal varices, ascites, and hepatorenal syndrome.

## 4.1 Normal Liver Physiology

The liver is a complex organ comprised of multiple types of cells responsible for its many physiologic functions including hepatocytes, hepatic sinusoidal endothelial cells, Kupffer



cells, intrahepatic lymphocytes, biliary cells and stellate cells. Important functions of the liver include protein synthesis and degradation, carbohydrate metabolism, lipid metabolism, detoxification and involvement in the innate immune system. This section will focus on the physiology of normal portal circulation in order to provide a basis for understanding the pathophysiologic disturbances that occur as a result of portal hypertension.

#### 4.1.1 Normal Portal Circulation

The circulatory system of the normal liver is a unique system characterized by a high compliance, low resistance system that is tightly regulated and can accommodate changes in blood volumes to prevent significant increases to portal pressure. The liver has a dual blood supply through the portal vein and the hepatic artery. Blood delivered to the liver converges in vascular channels called hepatic sinusoids. The total blood supply is tightly regulated in order to maintain a constant hepatic flow. A compensatory interplay exists such that changes in the portal venous blood flow are counteracted by opposing changes in the hepatic arterial flow and is termed the hepatic arterial buffer response [1]. Dysregulation of sinusoidal hemodynamics contributes to the development of portal hypertension.

### 4.2 Acute Liver Failure

Acute liver failure (ALF) is defined as the rapid development of hepatocellular dysfunction, characterized by impaired synthetic function (INR >1.5) and hepatic encephalopathy, in the absence of preexisting liver disease and with an illness duration of <26 weeks. Etiology of ALF is an important predictor of prognosis. In the United States, the leading causes of ALF are acetaminophen hepatotoxicity, indeterminate causes, idiosyncratic drug reactions, and hepatitis B virus in descending order [2].

Acute liver failure carries a high morbidity and mortality and is associated with multi-organ failure. This manifests clinically as cardiovascular instability, circulatory dysfunction, coagulopathy, pulmonary edema, renal failure, and encephalopathy with possible development of cerebral edema. The pathophysiology for development of multi-organ failure in ALF is not completely understood. Evidence to date suggests that the predominant mechanism is through activation of systemic inflammatory responses (SIRS) that is associated with worsening encephalopathy and increased mortality [3]. After hepatocyte death there is a release of pro-inflammatory cytokines and damage associated molecular patterns (DAMPs), which trigger activation of immune cells and lead to a systemic inflammatory response [3]. Given this,

a target of therapy for ALF has been to limit the progression of multi-organ failure through modulation of the systemic inflammatory response. This has led to development of extracorporeal liver support systems as well as utilization of high-volume plasma exchange [4].

### 4.3 Acute on Chronic Liver Failure

Acute on chronic liver failure (ACLF) is a recently defined syndrome that is distinct from decompensated cirrhosis and acute liver failure with unique implications. It is well recognized that decompensated cirrhosis is associated with complications such as renal dysfunction, hepatic encephalopathy, and ascites. There has been discrepancy among different scientific groups regarding defining the specific diagnostic criteria for ACLF with regards to duration of illness and precipitating events [5]. The American Association for the Study of Liver Diseases (AASLD) describes it as an acute deterioration of pre-existing chronic liver disease associated with multi-organ failure and an increased mortality [5]. The Asian Pacific Association for the Study of the Liver (APASL) defines it as acute hepatic insult manifesting as jaundice and coagulopathy and complicated within 4 weeks by ascites and/or encephalopathy in a patient with chronic liver disease [6].

While this is an area of active investigation with evolving insight of the clinical and pathophysiological characterization of ACLF, it is uniformly recognized as acute decompensation of cirrhosis with multi-organ failure and a high short-term mortality rate, estimated at 28-days to be 30–40% [7]. The most common precipitating events of ACLF are bacterial infection and active alcohol abuse. However, a considerable number of cases do not have any identifiable triggers [7]. The presence or absence of an identifiable trigger appears to be unrelated to the short-term mortality rate.

Acute on chronic liver failure is a dynamic syndrome with a variable course, ranging from improvement in some to rapid progression with multi-organ failure and death in others. A study assessing the clinical course of 388 patients with ACLF over 28 days demonstrated that ACLF resolved in 49.5% of patients, had a steady course in 30.4%, and worsened in 20.1% [8]. The severity of the clinical course correlated with increased short-term mortality. ACLF can occur at anytime during the course of disease. A large prospective European study (CANONIC Study) [9] of 1343 patients who presented with decompensated cirrhosis, 415 of whom met criteria for ACLF, found that nearly half of patients identified as having ACLF did not have prior decompensation or had developed their first decompensation within the 3 months prior to development of ACLF. Furthermore, these patients had a more severe course than those with a long history of decompensated cirrhosis.



Acute on chronic liver failure is associated with multi-organ failure and SIRS. Data from the CANONIC study demonstrates a significantly higher white cell count as well as C-reactive protein (CRP) when compared to those without ACLF. The degree of elevation of inflammatory markers is positively correlated with the grade of ACLF and worse outcomes [9, 10]. This observation provides the basis for further investigation of prognosis in ACLF using potential biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL). NGAL is a product of the lipocalin-2 gene (LCN2) that has been shown to be up-regulated in the setting of inflammatory conditions and liver injury. A recent study in patients with ACLF demonstrated that LCN2 is significantly up-regulated and urine NGAL levels are markedly elevated. Additionally urine NGAL is an independent predictor of 28-day mortality [11]. This offers a promising means of predicting mortality in patients with ACLF. In addition to utilizing markers of SIRS for prognostication, modulation of SIRS is also being evaluated as a targeted therapy in ACLF. Mookerjee et al., evaluated the use of non-selective beta blockers (NSBBs) as a means to dampen SIRS in 349 patients with ACLF and demonstrated that patients treated with NSBBs had lower grades of ACLF and significantly reduced short term mortality [12].

As is the case with decompensated cirrhosis, ACLF is characterized by hemodynamic abnormalities that lead to severe complications such as development of gastroesophageal varices, ascites, encephalopathy and hepatorenal syndrome. The marked circulatory dysfunction is a result of increased intrahepatic resistance as well as peripheral vasodilation that leads to a hyperdynamic circulatory state and portal hypertension. The pathophysiology and clinical consequences of portal hypertension will be the focus of the remainder of this chapter.

## 4.4 Portal Hypertension

### 4.4.1 Hemodynamics of Portal Hypertension

Portal hypertension is an important clinical entity that develops due to increased resistance to portal blood flow and can lead to important potentially lethal clinical complications such as variceal hemorrhage, ascites and hepatorenal syndrome. It is classified by the site of resistance and can be pre-hepatic, intra-hepatic or post-hepatic. In Western countries portal hypertension most commonly is a consequence of cirrhosis. Portal hypertension develops as a result of changes in portal resistance as well as in portal inflow, which is represented by Ohm's law:  $P = F \times R$ . Ohm's law describes the pressure gradient (P) in the portal circulation as a product of the portal flow (F) and resistance to flow (R) within the entire portal venous system. When applying this law to portal

hypertension, increases in both intrahepatic vascular resistance and splanchnic blood flow are the two main contributors to increased portal pressure [13].

### 4.4.2 Increased Intrahepatic Vascular Resistance

In portal hypertension due to cirrhosis, the increased intrahepatic vascular resistance is due to both fixed changes due to structural changes and dynamic variables relating to intrahepatic vasoconstriction.

There are several structural changes that play a pivotal role in increased vascular resistance in cirrhosis. Hepatic stellate cells are activated in response to hepatocellular injury and become contractile in an activated state. This exerts compressive effects on sinusoids leading to narrowing of the lumen. Additionally, activated stellate cells lead to deposition of collagen in the space of Disse resulting in a decrease in the area of the hepatic sinusoids [14, 15]. Furthermore, centrilobular venules are compressed by regenerating nodules and portal inflammation [16].

Additionally intrahepatic vasoconstriction due to impaired response to vasodilatory stimuli contribute to increased intrahepatic resistance. The two main factors are a decreased production of vasodilator nitric oxide (NO) and increased production of vasoconstrictors, such as endothelin 1 (ET-1) [17–19].

Nitrous Oxide is a potent vasodilator that results in relaxation of the sinusoidal vasculature and is paradoxically regulated in portal hypertension. Intrahepatic NO production decreases in cirrhosis and, as a result contributes to increased intrahepatic vascular resistance. NO is synthesized by nitric oxide synthase and freely penetrates cellular membranes and stimulates the cGMP-dependent protein kinase pathway leading to vascular relaxation [20, 21]. One of the isoforms of nitric oxide synthase is endothelial nitric oxide synthase (eNOS), which plays a key role in maintaining homeostasis. In cirrhosis, the reduced NO production by hepatic endothelial cells is a result of dysfunction within the eNOS system. Increases in oxidative stress, caveolin-1, RhoA, thromboxane A2, G-protein-coupled receptor kinase-2, and decreased AKT and BH4 activity are all factors involved in this dysfunction through defects in activation of eNOS [22]. The reduction in NO production results in reduced vasodilation and decreased ability to antagonize contractile factors, such as ET-1, which promotes hepatic stellate cell activation and constriction around sinusoidal blood vessels [23].

### 4.4.3 Increased Splanchnic Blood Flow

An increase in splanchnic blood flow is primarily determined by vasodilation of arterial splanchnic vessels. While

the mechanism is multifactorial in origin, the main contributor to arterial splanchnic vasodilation is an increase in NO production in the splanchnic circulation [24]. In contrast to intrahepatic NO, there is an overproduction of NO in the splanchnic vascular bed. Studies demonstrate upregulation of eNOS leads to increased NO release by the superior mesenteric arteries endothelium prior to the development of a hyperdynamic splanchnic circulation, suggesting that NO plays a role in development of increased inflow [24, 25]. The arterial vasodilation leads to a relative arterial hypovolemia, expansion of plasma volume and ultimately, to a hyperdynamic splanchnic circulatory state.

#### 4.4.4 Hyperdynamic Circulation

The hyperdynamic circulatory state is characterized by decreased systemic vascular resistance and high cardiac output [26]. As noted in the prior section, in cirrhosis there is an increase in peripheral endothelial production of local vasodilators as well as a decreased vascular response to vasoconstrictors, which results in systemic and splanchnic vasodilation, resulting in decreased effective circulating volume. The decrease in pressure sensed at cardiac and renal baroreceptors leads to activation of the sympathetic nervous system, renin-angiotensin-aldosterone system and antidiuretic hormone. This results in renal sodium and water retention and, ultimately, plasma volume expansion, which characterize the hyperdynamic circulatory state [21]. Sequelae of the portal hypertension and the hyperdynamic circulatory state, including gastroesophageal varices, ascites and hepatorenal syndrome, will be discussed in detail in the following sections.

### 4.5 Varices

#### 4.5.1 Formation of Portosystemic Collaterals and Gastroesophageal Varices

Portosystemic collateral vessels develop as a compensatory response to decompress the portal system and do so via opening of pre-existing vessels and angiogenesis. The more severe and prolonged the portal hypertension, the higher the number of portosystemic pathways but the physiologic stimuli responsible for initiating collateral formation is controversial. Traditionally, it was thought that the development of collateral circulation was due to passive opening of vascular channels as a result of portal hypertension [27]. More recent data suggests that the change in portal pressure is detected by intestinal microcirculation leading to generation of various angiogenic factors, most notably VEGF, that

results in angiogenesis driven formation of collateral circulation [27, 28].

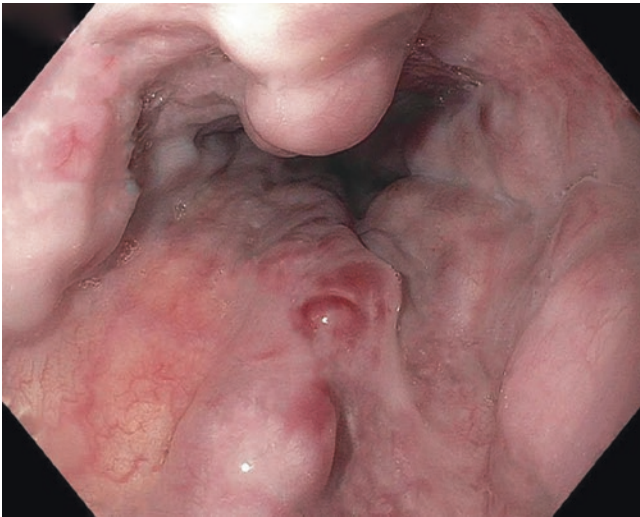
Varices can be found along the entire gastrointestinal tract in patients with portal hypertension. Common locations of portosystemic shunting occur between the left gastric vein and the esophageal veins, the short gastric veins and the splenic vein, the superior hemorrhoidal vein and the middle/inferior hemorrhoidal veins, and between the paraumbilical venous plexus and the subcutaneous veins in the anterior abdominal wall [29]. Communications between the left gastric vein and the esophageal-azygos veins and between the short gastric veins and the splenic vein are the collaterals primarily responsible for the development of gastroesophageal varices.

In patients with cirrhosis and portal hypertension, the normal vascular relations are significantly altered. Due to elevated pressures, blood from the portal venous system may reverse direction away from the liver and pass through the portosystemic collaterals, called hepatofugal flow. The increase in portal pressure leads to engorgement of the collateral vessels. This increased pressure creates a backpressure that is transmitted from the periesophageal veins on the visceral side of the bowel wall via penetrating vessels to the submucosal and subepithelial locations, leading to the development of varices. The development and dilation of collateral vessels is the pathophysiologic event that leads to the complication of variceal hemorrhage [30].

The degree of portal hypertension plays a key role in formation of varices as well as risk of rupture and hemorrhage. Hepatic vein pressure gradient (HPVG) is the difference between wedged hepatic venous pressure and the free hepatic venous pressure. It is a predictor for the severity of portal hypertension and correlates with the risk of variceal formation, hemorrhage, and prognosis [31]. Variceal formation and bleeding develops at an HPVG greater than 12 mmHg [32]. HPVG >20 mmHg has been shown to be predictive of failure to control bleeding as well as increased risk of early rebleeding [31].

#### 4.5.2 Risk of Variceal Hemorrhage

Bleeding from ruptured varices is a severe complication of portal hypertension. With progression of portal hypertension the intravariceal pressure increases, leading to increased size with wall thinning. When the expanding force is no longer counter-balanced by variceal wall tension there is resultant variceal rupture and bleeding. Thus, the key factor for variceal rupture is the wall tension of varices, or the force generated by the variceal wall, which is described by Laplace's Law. According to Laplace's Law,  $T = TP \times r/w$ , where  $T$  equals wall tension,  $TP$  equals transmural pressure,



**Fig. 4.1** Large esophageal varices in the distal lumen with “red wale” signs, portending a high-risk of variceal hemorrhage

$r$  is radius of the varix and  $w$  is width or thickness of the varix. Transmural pressure is the difference in the variceal and the esophageal luminal pressure [30]. When the wall tension reaches a critical point, rupture and hemorrhage occurs. Thus, patients with large, thin walled varices and elevated portal pressures have the highest risk of variceal hemorrhage (Fig. 4.1).

An additional risk factor for variceal hemorrhage is bacterial infection. There is a significant association between variceal bleed and bacterial infection. One hypothesis suggests that bacterial infection triggers a cytokine cascade leading to increased variceal pressure and therefore increased risk of variceal hemorrhage [33].

## 4.6 Ascites

### 4.6.1 Pathogenesis of Ascites

Ascites is the pathologic accumulation of intraperitoneal fluid. In the United States ascites is due to portal hypertension in 85% of cases [34]. Other causes include malignancy, heart failure, infections and nephrotic syndrome. This section will focus on cirrhotic ascites. It is a common complication of portal hypertension, developing in up to 50% of patients within 10 years of a diagnosis of compensated cirrhosis [35].

The most recognized and accepted theory explaining ascitic fluid formation, the “arterial vasodilation hypothesis”, describes the development of ascites as a complication of portal hypertension [36, 37]. The splanchnic vasodilation and reduced systemic vascular resistance (SVR) lead to decreased mean arterial pressure (MAP)

[15]. Progressive vasodilation with marked reduction in systemic vascular resistance cannot be effectively compensated by increases in cardiac output (CO) and therefore, leads to a reduced effective circulating volume. In response to the reduction in pressure at the carotid and renal baroreceptors there is a compensatory activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and antidiuretic hormone. The net effect of these neurohormonal mechanisms is an increase in sodium and water retention resulting in expansion of the extracellular fluid. Increased hydrostatic pressure in the splanchnic capillaries and increased vascular wall permeability, as well as decreased oncotic pressure in the setting of hypoalbuminemia lead to the excess extracellular fluid accumulates in the peritoneal cavity [36, 38].

### 4.6.2 Spontaneous Bacterial Peritonitis

A potentially lethal complication of ascites is the development of an ascitic fluid infection called spontaneous bacterial peritonitis (SBP). Spontaneous bacterial peritonitis is a commonly encountered infection in cirrhosis and is associated with hepatic decompensation and SIRS resulting in multi-organ failure [39]. In hospital mortality associated with SBP is 30–50% [40]. Gram-negative gut flora, particularly *Escherichia coli* and *Klebsiella* species, are isolated in 70% of cases of culture positive SBP. Gram-positive streptococcus and staphylococcus species account for the majority of the remaining isolates [40]. Analysis of the ascitic fluid by performing a diagnostic paracentesis is required to make the diagnosis, and is defined as a polymorphonuclear cell count  $\geq 250$  cells/mm<sup>3</sup>. The diagnosis should be suspected in patients that present with fever, altered mental status, abdominal pain or tenderness, or hypotension. However patients with ascites admitted to the hospital with other symptoms should also be tested.

Although not completely understood, the proposed pathogenesis of SBP involves overgrowth of gut bacteria and enhanced permeability of the bowel wall, which results in translocation of bacteria from the intestinal lumen to mesenteric lymph nodes [41, 42]. In non-cirrhotic individuals, local immune defenses kill bacteria that colonize lymph nodes. In cirrhosis, impairment in immune defense mechanisms, including the reticuloendothelial system and humoral and cell-mediated immunity, results in spread of bacteria to the systemic circulation followed by entry into the hepatic lymph and seeding of the ascitic fluid resulting in SBP [43, 44]. In addition, the increase in circulating endotoxin levels leads to release of cytokines and results in increased systemic inflammation. The heightened systemic inflammatory response is associated with increased mortality [45, 46].

### 4.6.3 Renal Vasoconstriction and Hepatorenal Syndrome

Hepatorenal syndrome is an important clinical complication of portal hypertension that is a unique form of renal failure and is associated with a poor prognosis [47]. Hepatorenal syndrome is defined by presence of cirrhosis with ascites, serum creatinine greater than 1.5 mg/dl, no improvement in serum creatinine after 2 days of diuretic withdrawal and volume expansion, absence of shock, and absence of offending nephrotoxic drugs or underlying parenchymal kidney disease [34]. Hepatorenal syndrome is not considered an intrinsic renal disease but rather is a consequence of decreased renal perfusion. Reduced effective circulating volume leads to a compensatory activation in the sympathetic nervous system and the renal vasoconstriction system. This results in progressive renal hypoperfusion. The decline in renal perfusion is associated with a reduction in glomerular filtration rate and can lead to development of the hepatorenal syndrome. Translocation of bacteria from the gut leads to a chronic inflammatory state and plays a key role in progression of disease.

## 4.7 Questions and Answers

1. A 60 year old former intravenous drug user was found to have elevated liver enzymes. Further testing revealed he was positive for hepatitis C. A liver biopsy showed bridging fibrosis and nodule formation. Which type of cell is activated in fibrosis progression?
  - A. Kupffer cells
  - B. Stellate cells
  - C. Pit cells
  - D. Cholangiocytes
  - E. Sinusoidal cells
2. What correctly describes the mechanisms involved in portal hypertension?
  - A. Increased splanchnic vasoconstriction and decreased portal inflow
  - B. Decreased splanchnic vasoconstriction and increased portal inflow
  - C. Increased splanchnic vasodilatation and decreased portal inflow
  - D. Increased splanchnic vasodilatation and increased portal inflow
  - E. None of the above
3. When should a diagnostic paracentesis be performed on a cirrhotic patient?
  - A. Admission to hospital
  - B. New onset ascites
  - C. Hypothermia
  - D. Mental status changes

- E. All of the above
4. Acute liver failure is associated with circulatory dysfunction and multi-organ failure. The primary pathophysiology is believed to be secondary to:
    - A. activation of the sympathetic nervous system and bacterial translocation
    - B. activation of the systemic inflammatory response syndrome
    - C. downregulation of the lipocalin-2 gene
    - D. activation of renin-angiotensin-aldosterone system
    - E. upregulation of baroreceptors

## 4.7.1 Answers

1. **B.** Stellate cell activation leads to contraction leading to increased sinusoidal pressure as well as collagen deposition in the space of Disse.
2. **D.** The product of increased splanchnic vasodilatation and increased portal inflow results in portal hypertension, as defined by Ohm's law.
3. **E.** All of the listed criteria are indications for performing a diagnostic paracentesis to test for the presence of spontaneous bacterial peritonitis.
4. **B.** In acute liver failure, both cerebral edema and multiorgan system failure are thought to be precipitated by SIRS and can lead to sepsis and high mortality.

## References

1. Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. *World J Gastroenterol.* 2010;16(48):6046–57.
2. Lee WM, et al. Acute liver failure: summary of a workshop. *Hepatology.* 2008;47(4):1401–15.
3. Chung RT, et al. Pathogenesis of liver injury in acute liver failure. *Gastroenterology.* 2012;143(3):e1–7.
4. Larsen FS, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol.* 2016;64(1):69–78.
5. Jalan R, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology.* 2014;147(1):4–10.
6. Sarin SK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int.* 2009;3(1):269–82.
7. Arroyo V, et al. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *J Hepatol.* 2015;62(1 Suppl):S131–43.
8. Gustot T, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology.* 2015;62(1):243–52.
9. Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144(7):1426–37. 1437.e1–9
10. Jalan R, et al. Acute-on-chronic liver failure: a distinct clinical condition. *Semin Liver Dis.* 2016;36(2):107–8.
11. Ariza X, et al. Neutrophil gelatinase-associated lipocalin is a biomarker of acute-on-chronic liver failure and prognosis in cirrhosis. *J Hepatol.* 2016;65(1):57–65.



12. Mookerjee RP, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol*. 2016;64(3):574–82.
13. Cichoz-Lach H, et al. Pathophysiology of portal hypertension. *J Physiol Pharmacol*. 2008;59(Suppl 2):231–8.
14. Reeves HL, Friedman SL. Activation of hepatic stellate cells—a key issue in liver fibrosis. *Front Biosci*. 2002;7:d808–26.
15. Iwakiri Y. Endothelial dysfunction in the regulation of cirrhosis and portal hypertension. *Liver Int*. 2012;32(2):199–213.
16. Nagula S, et al. Histological-hemodynamic correlation in cirrhosis—a histological classification of the severity of cirrhosis. *J Hepatol*. 2006;44(1):111–7.
17. Moller S, et al. Endothelin-1 and endothelin-3 in cirrhosis: relations to systemic and splanchnic haemodynamics. *J Hepatol*. 1995;23(2):135–44.
18. Gupta TK, et al. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology*. 1998;28(4):926–31.
19. Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. *J Hepatol*. 2007;46(5):927–34.
20. Battista S, et al. Hyperdynamic circulation in patients with cirrhosis: direct measurement of nitric oxide levels in hepatic and portal veins. *J Hepatol*. 1997;26(1):75–80.
21. Bolognesi M, et al. Splanchnic vasodilation and hyperdynamic circulatory syndrome in cirrhosis. *World J Gastroenterol*. 2014;20(10):2555–63.
22. Dimmeler S, et al. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature*. 1999;399(6736):601–5.
23. Perri RE, et al. Defects in cGMP-PKG pathway contribute to impaired NO-dependent responses in hepatic stellate cells upon activation. *Am J Physiol Gastrointest Liver Physiol*. 2006;290(3):G535–42.
24. Wiest R, Groszmann RJ. Nitric oxide and portal hypertension: its role in the regulation of intrahepatic and splanchnic vascular resistance. *Semin Liver Dis*. 1999;19(4):411–26.
25. Cahill PA, et al. Increased endothelial nitric oxide synthase activity in the hyperemic vessels of portal hypertensive rats. *J Hepatol*. 1996;25(3):370–8.
26. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther*. 2001;89(3):221–31.
27. Moreau R. VEGF-induced angiogenesis drives collateral circulation in portal hypertension. *J Hepatol*. 2005;43(1):6–8.
28. Fernandez M, et al. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. *J Hepatol*. 2005;43(1):98–103.
29. Sharma M, Rameshbabu CS. Collateral pathways in portal hypertension. *J Clin Exp Hepatol*. 2012;2(4):338–52.
30. Paquet KJ. Causes and pathomechanisms of oesophageal varices development. *Med Sci Monit*. 2000;6(5):915–28.
31. Moitinho E, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology*. 1999;117(3):626–31.
32. Garcia-Tsao G, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology*. 1985;5(3):419–24.
33. Hou MC, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology*. 2004;39(3):746–53.
34. Runyon BA, Committee APG. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49(6):2087–107.
35. Gines P, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology*. 1987;7(1):122–8.
36. Sola E, Gines P. Renal and circulatory dysfunction in cirrhosis: current management and future perspectives. *J Hepatol*. 2010;53(6):1135–45.
37. Schrier RW, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology*. 1988;8(5):1151–7.
38. Moore CM, Van Thiel DH. Cirrhotic ascites review: pathophysiology, diagnosis and management. *World J Hepatol*. 2013;5(5):251–63.
39. Such J, Runyon BA. Spontaneous bacterial peritonitis. *Clin Infect Dis*. 1998;27(4):669–74. quiz 675–6.
40. Almeida J, et al. Gut flora and bacterial translocation in chronic liver disease. *World J Gastroenterol*. 2006;12(10):1493–502.
41. Garcia-Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. *Best Pract Res Clin Gastroenterol*. 2004;18(2):353–72.
42. Pascual S, et al. Intestinal permeability is increased in patients with advanced cirrhosis. *Hepato-Gastroenterology*. 2003;50(53):1482–6.
43. Guarner C, Runyon BA. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, and management. *Gastroenterologist*. 1995;3(4):311–28.
44. Bernardi M. Spontaneous bacterial peritonitis: from pathophysiology to prevention. *Intern Emerg Med*. 2010;5(Suppl 1):S37–44.
45. Bolognesi M, et al. Clinical significance of the evaluation of hepatic reticuloendothelial removal capacity in patients with cirrhosis. *Hepatology*. 1994;19(3):628–34.
46. Twilla JD, et al. Severity of systemic inflammatory response syndrome affects outcomes in decompensated cirrhotics with spontaneous bacterial peritonitis. *Am J Gastroenterol*. 2016;111(7):1043–5.
47. Gines P, et al. Hepatorenal syndrome. *Lancet*. 2003;362(9398):1819–27.

## Further Reading

- Runyon, B. Management of adult patients with ascites due to cirrhosis: update 2012. AASLD practice guideline. [http://aasld.org/sites/default/files/guideline\\_documents/141020\\_Guideline\\_Ascites\\_4UFb\\_2015.pdf](http://aasld.org/sites/default/files/guideline_documents/141020_Guideline_Ascites_4UFb_2015.pdf).
- Garcia-Tsao, G et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016. Practice guidance by AASLD. <http://onlinelibrary.wiley.com/doi/10.1002/hep.28906/epdf>.



Kai Singbartl

**Abstract**

Interactions between the liver and the kidneys are complex and convoluted. Many primary disorders of liver disease have direct and immediate effects on renal physiology and function. Kidney injury and dysfunction are frequent problems in patients with acute liver failure. However, the etiology of acute kidney injury in patients with acute liver failure is usually multifactorial and involves insults similar to those seen in the general acute kidney injury population.

Chronic progressive liver disease (cirrhosis) modulates and is directly modulated by changes in systemic and renal hemodynamics, inflammatory response, renal handling of sodium, free water excretion, and other non-vasomotor mechanisms. Subsequent complications, e.g., worsening ascites, hyponatremia, and acute kidney injury, often complicate the care of patients with chronic progressive liver disease and increase their morbidity and mortality. This chapter will offer a basic understanding as to how chronic liver disease affects renal function, providing the theoretical foundation to further improve the care of patients with chronic progressive liver disease.

**Keywords**

Acute liver disease • Chronic liver disease • Renal function • Hyponatremia • Ascites

**5.1 Acute Liver Failure and the Kidney**

Approximately 80% of all patients with acute liver failure will also develop acute kidney injury [1, 2]. Almost half of these patients will ultimately need renal replacement therapy. Ischemic hepatitis or acetaminophen intoxication represent the underlying etiology in the majority of cases of acute liver failure that will also develop acute kidney injury.

Similar to the general acute kidney injury population, the etiology of acute kidney injury in patients with acute liver failure is multifactorial, including sepsis, nephrotoxins, ischemia/reperfusion, and hypovolemia [3]. However, acetaminophen, the most frequent cause for acute liver failure in the United States, has also direct nephrotoxic effects [4]. Acetaminophen nephrotoxicity shows characteristics similar to those seen in acute tubular necrosis: Granular casts can be found in the urine, urine osmolality is similar to that of plasma, urine sodium is  $>20$  mmol/L. The nephrotoxic effects of acetaminophen are directly related to the ingested dose. With increasing acetaminophen dose, sulfate and glutathione stores become depleted, shunting acetaminophen metabolism to the CYP-450 mixed function oxidase system in both liver and kidney. Resulting active intermediates, e.g. N-acetyl-p-benzoquinone imine, form adducts on moieties on cellular proteins which in turn activate caspases and lysosomal enzymes that initiate apoptosis or lead to cell necrosis [4].

K. Singbartl, M.D., M.P.H., F.C.C.M.  
Department of Critical Care Medicine, Mayo Clinic,  
Phoenix, AZ, USA

Center for Critical Care Nephrology, Department of Critical Care  
Medicine, University of Pittsburgh, Pittsburgh, PA, USA  
e-mail: [ks.ms@posteo.de](mailto:ks.ms@posteo.de)

## 5.2 Chronic Liver Disease and the Kidney: Introduction

Changes in renal function and physiology during chronic progressive liver disease are the result of complex circulatory, inflammatory, and vasomotor changes (Fig. 5.1). Patients with progressive cirrhosis demonstrate hemodynamic instability, characterized by reduced systemic vascular resistance secondary to splenic arterial vasodilation resulting from portal hypertension. Activation of several compensatory vasoconstrictive systems is necessary to maintain sufficient arterial blood pressure but also carries harmful effects on the kidney. These changes or (overzealous) medical treatment lead to alternate/impaired renal handling of sodium and water excretion as well as dysregulation of acid-base homeostasis.

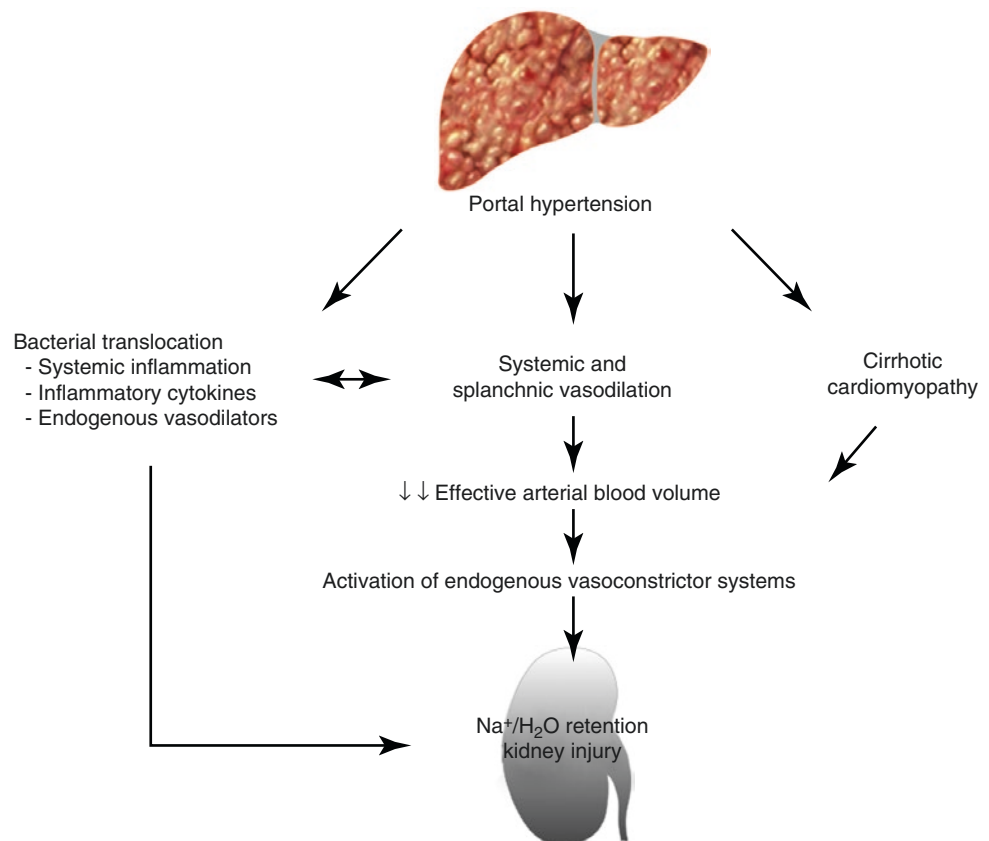
At a later stage, overwhelming compensatory vasoconstrictor mechanisms will also trigger intra-renal vasoconstriction, decreasing glomerular filtration rate and ultimately leading to acute kidney injury (further discussed elsewhere in this book).

Recent experimental and clinical research have also shed some light on intestinal bacterial translocation and ensuing systemic inflammation as potential contributors

to hemodynamic instability in patients with advanced cirrhosis [5, 6].

## 5.3 Systemic Hemodynamic Changes

Systemic hemodynamic instability, characterized by arterial and splanchnic vasodilation, is a classical hallmark of progressive liver disease with portal hypertension [7]. Worsening reduction in systemic vascular resistance gives rise to relative arterial hypovolemia. Initially, there is also an increase in cardiac output, largely due to a decrease in afterload. With deteriorating cirrhosis, some patients develop cirrhotic cardiomyopathy. Characteristics of cirrhotic cardiomyopathy are impaired diastolic relaxation, ECG changes (QT prolongation), enlarged left atrium, increased left ventricular wall thickness, and attenuated contractile responsiveness to stress [8]. Cirrhotic cardiomyopathy does usually not become clinically apparent until the reduction in left ventricular afterload and other compensatory mechanisms become insufficient to offset the reduction in left ventricular function. At this time, the cardiac output begins to decrease, and patients start to show symptoms of heart failure. The decline in cardiac output puts kidneys and liver at risk for additional damage.



**Fig. 5.1** Current concept and pathways of cirrhosis-induced changes in kidney function

## 5.4 Vasodilation

Intensified synthesis of circulating vasodilators, including prostaglandins, glucagon, vasoactive intestinal peptide, substance P, platelet activating factor and nitric oxide, plays a crucial role in the development of systemic arterial and splanchnic vasodilation in patients with progressive cirrhosis [9, 10]. This process increases with worsening cirrhosis [5]. Early on, systemic vasoconstrictive systems become activated. The renin-angiotensin-aldosterone system and the sympathetic nervous system represent the “first line of defense” under these circumstances. Non-osmotic hypersecretion of antidiuretic hormone occurs during later stages. Although the activation of vasoconstrictive system is necessary to stabilize the effective arterial blood volume and blood pressure, they are harmful to the kidneys, especially with respect to sodium and free water retention (see below) [5].

Currently available evidence suggests a particularly important role for nitric oxide in the development of splanchnic vasodilation during progressive cirrhosis and portal hypertension. Nitric oxide controls both the sinusoidal (intra-hepatic) and systemic/splanchnic circulations. Whereas nitric oxide deficiency in the liver raises intra-hepatic resistance, increased systemic levels of nitric oxide facilitate an overall hyperdynamic state [11].

Nitric oxide-mediated vasodilation rests with the activation of nitric oxide synthase in endothelial cells. This process is multifactorial. Several, different stimuli have been implicated, e.g. shear stress, vascular endothelial growth factors, tumor necrosis factor alpha, LPS, or bacterial DNA [12]. However, available data indicates that the interactions between the different vasoactive systems involved are too complex for one factor to be solely responsible for splanchnic vasodilation under these circumstances.

Some studies also have also pointed at an important role for persistent endotoxemia and ensuing systemic inflammation in the increased systemic prostacyclin synthesis. Here, portal systemic shunting and a defective reticular endothelial cell system are thought to cause impaired bacterial clearance, giving rise to bacteremia and endotoxemia [6].

Antidiuretic hormone also causes a strong intraregional vasoconstriction with subsequent reduction of the glomerular filtration rate [5].

---

## 5.5 Antidiuretic Hormone and Water Balance

Under normal circumstances, the body exerts tight control over total body water and osmolality. The release of antidiuretic hormone, also known as arginine vasopressin, from the hypothalamus is the primary regulator of serum osmolality [12]. Changes in plasma osmolality and volume in turn are the

two major stimuli for secretion of antidiuretic hormone [12]. An increase or decrease in serum osmolality directly leads to an increase or decrease, respectively, in the secretion of antidiuretic hormone. However, most cirrhotic patients demonstrate low serum osmolality and sodium concentrations, making elevated osmotic stimulation of antidiuretic hormone secretion in this situation unlikely. Non-osmotic secretion of antidiuretic hormone involves the autonomic nervous system and its baroreceptors (see below). The fact that urine osmolality is higher than plasma osmolality indicates that under physiologic conditions the kidneys remain in an antidiuretic state.

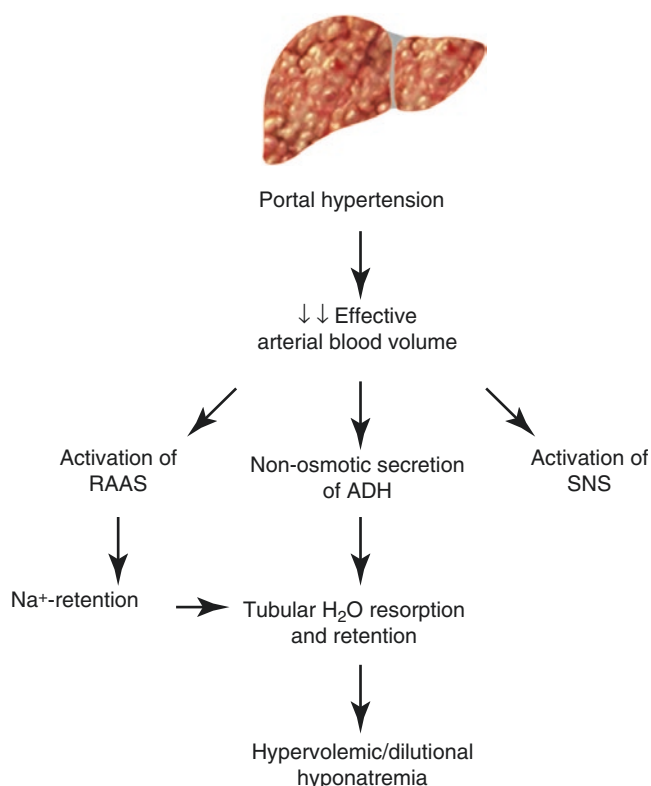
Antidiuretic hormone acts by modulating water permeability in the renal collecting ducts. Antidiuretic hormone binds to vasopressin 2 receptors on the baso-lateral membrane of epithelial cells along the renal collecting ducts, enhancing the production of cyclic AMP and activation of protein kinase A. Phosphorylation of microtubular subunits will then allow for the aggregation and subsequent translocation of water channel proteins (aquaporins) to the apical plasma membrane [13]. Here, aquaporins facilitate the reabsorption of water from the collecting duct, raising body water content. A decrease in serum osmolality results in inactivation of renal aquaporin channels and excretion of diluted urine, preserving body water/volume status and serum osmolality.

---

## 5.6 Sodium and Water Homeostasis in Chronic Liver Disease

Although total body water content is not affected in cirrhotic patients at first, there is a shift of fluid to the extracellular space, which in turn leads to a decrease in intravascular volume. Subsequent decrease in blood pressure stimulates carotid baroreceptors which together with reduced renal blood flow activate renin-angiotensin-aldosterone and sympathetic nervous systems. There is also enhanced non-osmotic production of antidiuretic hormone (ADH) under these circumstances (see above). Hypervolemic or dilutional hyponatremia is a consequence of impaired solute-free water excretion by the kidneys leading to disproportionate retention of water over sodium (Fig. 5.2) [14].

Despite these well-established mechanisms of hyponatremia in patients with cirrhosis, other mechanisms or pathways have to be considered in the evaluation of cirrhotic patients with hyponatremia [14]. Hypovolemic hyponatremia can develop due to renal (e.g., excessive diuresis) or extra-renal losses (e.g., diarrhea due to excessive use of lactulose or due to infection-associated diarrhea) [15]. Patients with cirrhosis sometimes also develop poor salt and protein intake [16]. This will impair the kidney's ability to excrete solutes and free water. Endocrine disorders, cardiac disease, infections, drugs and toxins all can cause hyponatremia in patients with chronic liver disease but are beyond the scope of this chapter [14].



**Fig. 5.2** Development of hypervolemic/dilutional hyponatremia in liver cirrhosis

### 5.6.1 Ascites Formation

Uncontrolled sodium and water retention in cirrhotic patients leads to ascites formation. Only persistent fluid and sodium restriction can prevent this.

Reduced renal blood flow and subsequent renal vasoconstriction result in decreased glomerular filtration rate. At the same time, hypersecretion of antidiuretic hormone induces the formation and intracellular trafficking of aquaporin channels within epithelial cells of the collecting duct system. This together with a diminished glomerular filtration rate hinders the elimination of solute-free water by the kidneys, leading to hypotonic hyponatremia. Although total body water remains unchanged under the circumstances, fluid begins to shift to the extracellular space, resulting in ascites formation and further intravascular hypovolemia.

### 5.6.2 Hyponatremia

Up to 50% of patients with cirrhosis display serum sodium levels  $<135$  mmol/L, and more than 20% reveal serum sodium concentrations  $<130$  mmol/L [17].

Hyponatremia is a key marker of poor prognosis, especially if the MELD score is low [18, 19]. Hyponatremia is

associated with an up to eightfold increase risk of dying before liver transplant. However, hyponatremia is considered a marker of severity of cirrhosis and its complications rather than an actual mediator of poor outcome.

Patients with hyponatremia usually do not become symptomatic unless there is a sudden, drastic drop in serum sodium concentrations or their serum concentration is less than 125 mmol/L. Patients will initially present with minor symptoms, e.g. nausea, headache.

Hyponatremia in patients with chronic progressive liver disease is usually a slowly evolving process, permitting the brain to adapt to a hypoosmolar environment. It is the acuity of hyponatremia rather than the extent of hyponatremia that determines the severity of neurological deficits.

## 5.7 Acid-Base Disorders

The development of metabolic acidosis is a frequent occurrence in patients with chronic liver disease [3]. Metabolic acidosis can occur even in the setting of preserved renal function. Both anion gap metabolic acidosis (ketoacidosis, lactic acidosis) and non-anion gap acidosis occur in patients with chronic liver disease.

### 5.7.1 Lactic Acidosis

The so-called type A lactic acidosis is the result of tissue hypoperfusion and subsequent increase in anaerobic glycolysis. It is frequently seen in patients with decompensated chronic liver disease, in particular in the setting of hemorrhage or sepsis [20].

Type B lactic acidosis can develop in the absence of tissue hypoperfusion. Although lactate production is normal under these circumstances, liver dysfunction leads to decreased lactate utilization and consequently lactic acidosis [20].

### 5.7.2 Ketoacidosis

Patients with chronic (alcoholic) liver disease often suffer from a reduced caloric intake and/or volume depletion, resulting from vomiting after consuming extreme amounts of alcohol. In the liver, ethanol is oxidized to acetaldehyde. The ketone bodies acetoacetic acid and  $\beta$ -hydroxybutyrate represent the end products of acetaldehyde metabolism, resulting in anion gap metabolic acidosis [21].

### 5.7.3 Non-anion Gap Metabolic Acidosis

Diarrhea: lactulose therapy is a cornerstone of treatment for hepatic encephalopathy. Side effects of lactulose therapy

include diarrhea with subsequent bicarbonate losses through the stool, giving rise to an anion gap metabolic acidosis [20].

**Renal tubular acidosis:** If the kidneys cannot excrete the daily acid load anymore, renal tubular acidosis will develop. Distal renal tubular acidosis can evolve in patients with chronic liver disease due to an inborn distal tubular acidification defect associated with autoimmune hepatic diseases, e.g. primary biliary cirrhosis [22]. Also, the reduction in effective circulating blood volume seen in patients with chronic liver disease results in attenuated delivery of sodium to the distal tubular system. Impaired sodium delivery to the distal tubular system leads to impaired distal tubular acidification. Restoration of normal sodium delivery to the distal tubular system will correct the defect in the distal tubular acidification [20].

#### 5.7.4 Treatment

Treatment of metabolic acidosis in patients with chronic liver disease is similar to that in other patients [3]. Primary goal is the correction of the underlying etiology (see above). This will include discontinuation of harmful medication, resuscitation to achieve sufficient systemic hemodynamics, thiamine administration, modification of treatment with laxatives, and administration of sodium bicarbonate.

### 5.8 Non-vasomotor Effects on Renal Function in Patients with Cirrhosis

#### 5.8.1 Bile Cast Nephropathy

With worsening liver function, cirrhotic patients also display increased serum concentration of bilirubin and bile acid. Intra-renal bile casts can form under these circumstances and impair proximal tubular function [6, 23]. As liver function improves and/or bile and bilirubin levels return to normal, renal function will also begin to improve. The exact time point of bile cast formation in the overall disease process is unknown. However, high concentrations of bilirubin (>20 mg/dL) for a prolonged period of time are usually seen in patients with bile cast nephropathy. Bile cast nephropathy can occur in patients without cirrhosis.

As bile cast nephropathy can only be diagnosed by means of a kidney biopsy, it is often forgotten in the differential diagnosis of renal dysfunction in patients with chronic progressive liver disease. However, the current approach to renal dysfunction in cirrhotic patients appears to be incomplete, as long as it does not include bile cast nephropathy as potential underlying etiology [23].

#### 5.8.2 Intra-abdominal Hypertension

Intra-abdominal pressure >12 mmHg defines intra-abdominal hypertension [24]. Subsequent decline in renal perfusion is considered the main mechanism for renal dysfunction during intra-abdominal hypertension [25]. Following initial preservation of glomerular filtration rate due to autoregulatory mechanisms, later changes in intra-renal hemodynamics may also contribute to an additional decrease in renal function. Here, a drop in glomerular hydrostatic pressure (due to decreased renal perfusion) and a simultaneous rise in the hydrostatic pressure within the Bowman capsule (due to intra-abdominal hypertension itself) will further reduce glomerular filtration rate [25].

A mechanistic link between intra-abdominal hypertension and renal dysfunction in patients with cirrhosis and subsequent ascites has been postulated for a long time [6, 26]. Lowering intra-abdominal pressure below 12 mmHg has been associated with improved glomerular filtration rate, renal blood flow, and urine output. Moreover, placement of a peritoneal venous shunt in cirrhotic patients with ascites to maintain low intra-abdominal pressures has also resulted in improved glomerular filtration rate and renal blood flow [26]. However, simply lowering intra-abdominal pressure in the setting of massive ascites without adequate hemodynamic stabilization, i.e. fluid resuscitation during large-volume paracentesis, will actually worsen renal function rather than improve it [27].

#### 5.8.3 Inflammatory Changes

The development of a systemic inflammatory response syndrome in patients with cirrhosis is strongly associated with onset of renal dysfunction and overall poor outcome [28]. Numerous animal studies and a few clinical studies have allowed us to identify two molecules that appear to play a key role in the development of renal dysfunction in chronic progressive liver disease with ensuing systemic inflammation [6].

Toll-like receptor 4 activation gives rise to an increased production of other pro-inflammatory mediators. Renal toll-like receptor 4 expression, in particular that in the proximal renal tubules, is upregulated during experimental cirrhosis [29]. Translocation of intestinal bacteria is thought to promote up regulation of toll-like receptor 4. Consequently, selective gut decontamination with norfloxacin led to decreased toll-like receptor 4 expression, improved renal histology, and kidney function tests [30]. Patients with liver cirrhosis also reveal upregulated toll-like receptor 4 expression in renal tubular cells during infection/inflammation [29].

Interleukin 17A is secreted by T cells and intestinal paneth cells in response to infectious/inflammatory stimuli. Experimental models of hepatic ischemia-reperfusion have shown that neutralizing interleukin 17A prevents renal dysfunction in this situation.



## 5.9 Summary

Here, we have presented conventional and new, evolving concepts on the effects of acute and chronic liver disease on renal (patho-) physiology. Available research shows that renal pathophysiology during (chronic) liver disease is complex and involves more than just vasomotor dysfunction. Systemic inflammation in particular has emerged as a new key mediator in kidney injury and dysfunction under these circumstances.

Worsening cirrhosis has detrimental effects on kidney function and subsequent fluid and electrolyte homeostasis. Ascites formation is a consequence of both liver and kidney dysfunction. Hyponatremia is a serious complication in patients with progressive cirrhosis and represents an important predictor of mortality. However, hyponatremia itself is rarely the cause of death in cirrhotic patients. It should therefore only be corrected when it becomes severely symptomatic or life threatening.

## References

1. Tujios SR, Hynan LS, Vazquez MA, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. *Clin Gastroenterol Hepatol*. 2015;13:352–9. <https://doi.org/10.1016/j.cgh.2014.07.011>.
2. O'Riordan A, Brummell Z, Sizer E, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. *Nephrol Dial Transplant*. 2011;26:3501–8. <https://doi.org/10.1093/ndt/gfr050>.
3. Regner KR, Singbartl K. Kidney injury in liver disease. *Crit Care Clin*. 2016;32:343–55. <https://doi.org/10.1016/j.ccc.2016.03.005>.
4. Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. *J Med Toxicol*. 2008;4:2–6.
5. Solà E, Ginès P. Challenges and management of liver cirrhosis: pathophysiology of renal dysfunction in cirrhosis. *Dig Dis*. 2015;33:534–8. <https://doi.org/10.1159/000375344>.
6. Adebayo D, Morabito V, Davenport A, Jalan R. Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. *Kidney Int*. 2015;87:509–15. <https://doi.org/10.1038/ki.2014.338>.
7. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–90. <https://doi.org/10.1056/NEJMr0809139>.
8. Møller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J*. 2013;34:2804–11. <https://doi.org/10.1093/eurheartj/eh246>.
9. Matloff RG, Arnon R. The kidney in pediatric liver disease. *Curr Gastroenterol Rep*. 2015;17:36. <https://doi.org/10.1007/s11894-015-0457-x>.
10. Iwakiri Y. The molecules: mechanisms of arterial vasodilatation observed in the splanchnic and systemic circulation in portal hypertension. *J Clin Gastroenterol*. 2007;41(Suppl 3):S288–94. <https://doi.org/10.1097/MCG.0b013e3181468b4c>.
11. Hu LS. Current concepts on the role of nitric oxide in portal hypertension. *World J Gastroenterol*. 2013;19:1707. <https://doi.org/10.3748/wjg.v19.i11.1707>.
12. John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. *World J Gastroenterol*. 2015;21:3197–205. <https://doi.org/10.3748/wjg.v21.i11.3197>.
13. Jung HJ, Kwon T-H. Molecular mechanisms regulating aquaporin-2 in kidney collecting duct. *Am J Physiol Renal Physiol*. 2016;311:F1318–28. <https://doi.org/10.1152/ajprenal.00485.2016>.
14. Liamis G, Filippatos TD, Lontos A, Elisaf MS. Hyponatremia in patients with liver diseases: not just a cirrhosis-induced hemodynamic compromise. *Hepatol Int*. 2016;10:762–72. <https://doi.org/10.1007/s12072-016-9746-1>.
15. Liamis G, Filippatos TD, Elisaf MS. Correction of hypovolemia with crystalloid fluids: Individualizing infusion therapy. *Postgrad Med*. 2015;127:405–12. <https://doi.org/10.1080/00325481.2015.1029421>.
16. Berl T. Impact of solute intake on urine flow and water excretion. *J Am Soc Nephrol*. 2008;19:1076–8. <https://doi.org/10.1681/ASN.2007091042>.
17. Angeli P, Wong F, Watson H, et al. Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology*. 2006;44:1535–42. <https://doi.org/10.1002/hep.21412>.
18. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359:1018–26. <https://doi.org/10.1056/NEJMoa0801209>.
19. Sersté T, Gustot T, Rautou P-E, et al. Severe hyponatremia is a better predictor of mortality than MELDNa in patients with cirrhosis and refractory ascites. *J Hepatol*. 2012;57:274–80. <https://doi.org/10.1016/j.jhep.2012.03.018>.
20. Ahya SN, José Soler M, Levitsky J, Batlle D. Acid-base and potassium disorders in liver disease. *Semin Nephrol*. 2006;26:466–70. <https://doi.org/10.1016/j.semnephrol.2006.11.001>.
21. Rehman HU. A woman with ketoacidosis but not diabetes. *BMJ*. 2012;344:e1535. <https://doi.org/10.1136/bmj.e1535>.
22. Komatsuda A, Wakui H, Ohtani H, et al. Tubulointerstitial nephritis and renal tubular acidosis of different types are rare but important complications of primary biliary cirrhosis. *Nephrol Dial Transplant*. 2010;25:3575–9. <https://doi.org/10.1093/ndt/gfq232>.
23. van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int*. 2013;84:192–7. <https://doi.org/10.1038/ki.2013.78>.
24. Malbrain MLNG, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. *Intensive Care Med*. 2006;32:1722–32.
25. Villa G, Samoni S, De Rosa S, Ronco C. The pathophysiological hypothesis of kidney damage during intra-abdominal hypertension. *Front Physiol*. 2016;7:55. <https://doi.org/10.3389/fphys.2016.00055>.
26. Cade R, Wagemaker H, Vogel S, et al. Hepatorenal syndrome. Studies of the effect of vascular volume and intraperitoneal pressure on renal and hepatic function. *Am J Med*. 1987;82:427–38.
27. Umgelter A, Reindl W, Wagner KS, et al. Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial. *Crit Care*. 2008;12:R4. <https://doi.org/10.1186/cc6765>.
28. Cazzaniga M, Dionigi E, Gobbo G, et al. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol*. 2009;51:475–82. <https://doi.org/10.1016/j.jhep.2009.04.017>.
29. Shah N, Mohamed FE, Jover-Cobos M, et al. Increased renal expression and urinary excretion of TLR4 in acute kidney injury associated with cirrhosis. *Liver Int*. 2013;33:398–409. <https://doi.org/10.1111/liv.12047>.
30. Shah N, Dhar D, Zahraa Mohammed El F, et al. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol*. 2012;56:1047–53. <https://doi.org/10.1016/j.jhep.2011.11.024>.

Jeffrey DellaVolpe, Minjee Kim, Thomas P. Bleck,  
and Ali Al-Khafaji

## Abstract

Mental status changes in acute and chronic liver disease can account for a significant portion of ICU admissions and mortality. Much of the pathology associated with these conditions is associated with an inability to maintain adequate blood flow. Thus, an understanding of both normal cerebrovascular physiology as well as the physiology behind derangements seen in both acute and chronic liver failure can help lead to better understanding and optimized management of these critically ill patients.

## Keywords

Acute liver failure • Autoregulation • Cerebral perfusion pressure • Cerebral edema • Hepatic encephalopathy

Mental status changes in acute and chronic liver disease can account for a significant portion of ICU admissions and mortality. Much of the pathology associated with these conditions is associated with an inability to maintain adequate blood flow. Thus, an understanding of both normal cerebrovascular

physiology as well as the physiology behind derangements seen in both acute and chronic liver failure can help lead to better understanding and optimized management of these critically ill patients.

J. DellaVolpe, M.D., M.P.H.  
San Antonio Military Medical Center,  
Uniformed Services University of the Health Sciences,  
3551 Roger Brooke Dr., Fort Sam Houston, TX 78234, USA  
e-mail: [jeff.dellavolpe@gmail.com](mailto:jeff.dellavolpe@gmail.com)

M. Kim, M.D.  
Neuro Spine Intensive Care Unit, Division of Stroke and  
Neurocritical Care, Ken and Ruth Davee Department of Neurology,  
Northwestern University Feinberg School of Medicine,  
Northwestern Memorial Hospital,  
676 N. St. Clair St., Arkes Pavilion, Rm. 13-115, Chicago, IL, USA  
e-mail: [Mkim4@nm.org](mailto:Mkim4@nm.org)

T.P. Bleck, M.D., M.C.C.M.  
Rush Medical College, Rush University Medical Center,  
600 S Paulina Street, Suite 544AAC, Chicago, IL 60612, USA

A. Al-Khafaji, M.D., M.P.H., F.C.C.M. (✉)  
University of Pittsburgh School of Medicine,  
Room 613 Scaife Hall, 3550 Terrace Street,  
Pittsburgh, PA 15261, USA  
e-mail: [alkhafajia2@upmc.edu](mailto:alkhafajia2@upmc.edu); <https://www.ccm.pitt.edu>

## 6.1 Normal Regulation of Cerebrovascular Function

The brain receives a large amount of blood flow compared with other organ systems using around a fifth of available oxygen for normal function [1]. Thus, tight regulation of blood flow and oxygen delivery is critical to survival. Small decreases in cerebral blood flow can have deleterious effects, with inhibition of cerebral protein synthesis, extracellular accumulation of glutamate and lactate, and cellular fluid shifts observed with even modest decreases in cerebral blood flow [2]. Conversely, high flows are relatively poorly tolerated, due to breakdown of the blood brain barrier, fixed space inside the cranial vault, and the clinical consequences of hyperemia including altered mental status, seizures, and posterior reversible encephalopathy syndrome. Therefore, normal regulation is tightly controlled by a system of cerebral hemodynamics, autoregulation, segmental vascular resistance, and neural astrocyte regulation.

### 6.1.1 Mechanisms of Functional Hyperemia

Continual and adequate cerebral blood flow is maintained by several mechanisms. As with all vascular beds, regional flow throughout the brain is proportional to the difference between inflow and outflow pressure ( $\Delta P$ ) divided by the resistance to flow, as is demonstrated by Ohm's Law.

$$\text{Regional Flow} = \frac{\Delta P}{\text{Resistance}}$$

As it relates to cerebral blood flow,  $\Delta P$  is the cerebral perfusions pressure or the difference between the cerebral arterial pressure and cerebral venous pressure. Cerebral arterial pressure is driven by cardiac output and ultimately mean arterial pressure.

$$\text{Cerebral Blood Flow} = \frac{\text{Parterial} - \text{Pvenous}}{\text{Cerebral Vascular Resistance}}$$

Since cerebral venous pressure is usually relatively low (2–5 mmHg) and is directly influenced by intracranial pressure and to a lesser effect by central venous pressure. Thus under normal circumstances:

$$\text{Cerebral Blood Flow} = \frac{\text{MAP} - \text{ICP}}{\text{Cerebral Vascular Resistance}}$$

Therefore, while mean arterial pressure (MAP) and intracranial pressure (ICP) affect cerebral blood flow, under normal circumstances, when these values are within normal limits, the main determinant of cerebral blood flow is cerebral vascular resistance. Much like vascular beds outside of the central nervous system, this resistance can be characterized as a function of length of the vessel ( $L$ ), viscosity of the blood ( $\eta$ ), and inversely proportional to the radius to the fourth power, as characterized by Pouiseuille's equation:

$$\text{Resistance} = \frac{L \cdot \eta}{r^4}$$

While this equation assumes steady, laminar flow, the most readily modifiable and influential variable to cerebral blood flow is the radius of the vessel in question, as manifested by cerebral vasodilation and vasoconstriction.

## 6.2 Mechanisms for Modulating Cerebral Blood Flow

In order to accommodate the high metabolic rate of the entire brain, continuous blood flow has to be ensured, with augmentation of blood flow through vasodilation to metabolically active regions and reduction of blood flow through vasoconstriction to less metabolically active regions. A host of mechanisms exist for maintaining the varied levels of cerebral blood flow.

### 6.2.1 The Neurovascular Unit

Large cerebral arteries give rise to arterioles and microvasculature, which are densely innervated by perivascular nerves. These neurons, microvessels, and glia form a close anatomical and functional entity [3]. This unit functions in several ways to ensure constant blood flow as well as the ability to increase blood flow for cerebral activity and protect against high surges in blood pressure.

### 6.2.2 Direct Neuronal Signaling

Active neurons release neurotransmitters into the extracellular space, which can directly and indirectly influence vasodilation. In particular, this has been demonstrated with glutamate and gamma-aminobutyric acid (GABA). Glutamate does not directly influence vasodilation, but rather indirectly works through indirect mechanisms including nitric oxide synthase, COX-2, and others. GABA likely plays a more direct role in local vasodilation. Synaptic activity also causes the release of intracellular potassium following generation of action potentials, which also increases blood flow by a nitric oxide mediated process. Neuromodulators and neuropeptides other than GABA and glutamate are also released from non-synaptic portions of the neuron [4].

### 6.2.3 Indirect Neuronal Signaling

The mechanisms to increase blood flow to metabolically active areas of the central nervous system extend beyond direct neuronal signaling. Local vasodilation is also propagated by the dilation of upstream arterioles, which has been demonstrated in several tissue models [5, 6]. Additionally, there is contact between the nerve, blood vessels, and astrocytes, which can act both locally as well as upstream to increase blood flow. Stimulation of astrocytes raises astrocytic calcium and causes dilation of nearby arterioles [7, 8].

### 6.2.4 Large Arterial Vascular Resistance

While direct and indirect mechanisms exist for resistance to blood flow at the level of the neurovascular unit, the large intracranial and extracranial arteries such as the carotid and vertebral arteries are a major site of resistance and thus significantly contribute to overall cerebral vascular resistance. The resistance in these vessels is ultimately greater than that observed in other vascular beds.

A host of neurohumoral and direct signaling mechanisms exist which modulate the total resistance in these large arter-

ies, including activation of sympathetic nerves and increasing concentrations of circulating vasopressin and angiotensin. These changes in resistance allow for increased cerebral blood flow due to increased metabolic activity, or to low mean arterial blood pressure, which would otherwise lead to low cerebral perfusion pressure [9].

### 6.3 Autoregulation

While local vasodilation and vasoconstriction are essential for ensuring adequate blood flow for metabolically active neurons, the brain is also dependent on other processes that prevent fluctuations in overall perfusion pressure. There are many reasons for this requirement to tightly regulate cerebral circulation, to include the brain's relative lack of a local energy store, disproportionally high metabolic rate, and high energy requirements. However, this is also underscored by the dire consequences that exist with even small fluctuations in overall cerebral blood flow.

Adequate cerebral blood flow (around 50 mL for 100 g of brain tissue) exists within the range of a cerebral perfusion pressure of 60–160 mmHg [10, 11]. Cerebral metabolic rate determines the cerebral vascular resistance as mentioned above, thus driving the cerebral perfusion pressure, given a normal mean arterial pressure and intracranial pressure. This cerebral perfusion pressure is maintained despite alterations in mean arterial pressure largely through autoregulation (Table 6.1).

Autoregulation is a process that exists in multiple vascular beds, but which exerts an especially pronounced effect in the central nervous system. It modulates cerebrovascular resistance to allow for constant cerebral blood flow despite alterations that exist in cerebral perfusion pressure both as a function of intracranial pressure and mean arterial pressure. As CPP rises and falls beyond critical limits, autoregulation is lost and flow becomes dependent on the level of CPP.

**Table 6.1** Determinants of cerebral perfusion

Measurement	Definition
Cerebral blood flow	Blood supply to entire brain at one point in time
Cerebral perfusion pressure	Pressure gradient driving cerebral blood flow
Intracranial pressure	Total pressure in cranial vault
Cerebral metabolic rate	Total rate of O <sub>2</sub> consumption driving the total blood flow
Cerebral blood volume	Total amount of blood in a given amount of brain tissue
Mean arterial pressure	Average blood pressure throughout the body as a function of cardiac output and systemic vascular resistance

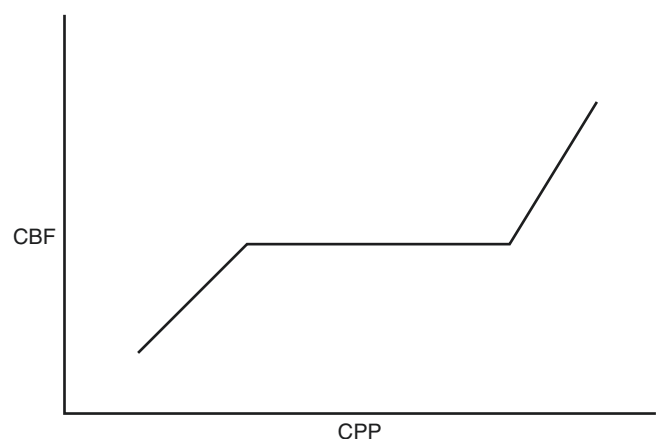
#### 6.3.1 Decreased Perfusion Pressure and Autoregulation

As CPP falls, vasodilation ensues to allow for adequate maintenance of cerebral blood flow. The mechanism is not completely defined but likely is attributed to a combination of neurogenic, myogenic, and metabolic responses. While not completely defined, this process likely mediated by nitric oxide and extracellular potassium. Regardless of the mechanism, this response has been accurately modeled to predict the clinical response [12] (Fig. 6.1).

The myogenic response refers to a change in vascular smooth muscle tone, inducing cerebral vasoconstriction with increases in extrinsic transmural pressure and vasodilation at lower perfusion pressures. This change has been demonstrated in cerebral blood vessels in as little as 1–3 s [13] and can be expected to maintain a consistent and adequate cerebral blood flow for arterial blood pressure ranges between 60 and 160 mmHg.

As perfusion continues to decrease, autoregulation is maintained through the release of metabolic factors. Amongst those implicated include potassium, hydrogen ion, adenosine, and oxygen [14, 15]. Hypoxia remains the dominant mechanism inducing cerebral blood vessel vasodilation by local mechanism as cerebral perfusion continues to fall [16].

As CPP continues to fall, autoregulation is lost resulting in decreases in cerebral blood flow. To a degree the clinical effect lags as cerebral metabolic rate is maintained due to increased oxygen extraction. As cerebral perfusion falls below the level of compensation by oxygen extraction, clinical signs of ischemia ensue. These can include altered mental status, dizziness, and cerebral vascular infarction. Cerebral oxygen consumption can be monitored by measuring of the oxygen content of venous blood through a jugular bulb catheter (see Sect. 6.7). However, the oxygen content of cerebral venous blood also depends on the ability of mitochondria to utilize oxygen.



**Fig. 6.1** Autoregulation curve. Cerebral blood flow (CBF) cerebral perfusion pressure (CPP)



### 6.3.2 Elevated Perfusion Pressure and Autoregulation

Elevations in cerebral blood flow can develop as cerebral perfusion pressure continues to rise. In a similar manner to decreases in cerebral perfusion pressure, autoregulation of cerebral blood flow is maintained at rising perfusion levels, largely through arteriolar vasoconstriction due to elevated transmural pressures. As with the changes associated with cerebral perfusion pressure, this vasoconstriction is not fully understood and likely multifactorial. However, there is a demonstrable role of endothelin-1 in the cerebral vasoconstriction of autoregulation [17, 18].

As mean arterial pressure continues to increase, cerebral perfusion pressure continues to rise past the point where vasoconstriction can limit cerebral blood flow. At critical pressures, there is a loss of myogenic vasoconstriction leading to a forced vasodilation known as autoregulatory breakthrough. This is now thought to be the critical event leading to rapidly elevated cerebral blood flow seen at the higher end of the autoregulatory curve [19, 20]. Clinical sequelae such as cerebral edema, hemorrhage, seizures, and posterior reversible leukoencephalopathy (PRES) can rapidly ensue [21].

## 6.4 Autoregulation and Liver Disease

While autoregulation can breakdown at both elevated and decrease levels of cerebral perfusion pressure, the primary mechanism seen in both acute and chronic liver disease is decreased cerebral perfusion pressure. As previously noted, cerebral perfusion pressure is a consequence of mean arterial pressure and intracranial pressure based on the following relationship:

$$CPP = MAP - ICP$$

Intracranial pressures can only be as low as physiologically normal levels (usually between 5 and 15 mmHg). Thus, while decreases in cerebral perfusion can exist because of either low arterial pressure *or* elevated ICP, increased cerebral perfusion can *only* exist because of elevated MAP.

Elevations in MAP are rare in both chronic and acute liver failure [22–24]. The reasons for this are multifactorial, including relative vasodilation, hyperdynamic circulation, and vasopressin deficiency [25]. Thus, any clinical evidence of high intracranial blood flow (intracranial hemorrhage, seizures, PRES) should prompt investigation for other causes in this population.

## 6.5 Cardiac Effect of Liver Failure on Cerebrovascular Physiology

Regardless of the chronicity of the liver failure, it exerts physiologic effects on both the circulatory and respiratory systems that play a role in the cerebrovascular physiology.

### 6.5.1 Circulatory Effects of Liver Disease

Liver failure is associated with a vasoplegic and hyperdynamic state. This progressive systemic vasodilation can be attributed to a variety of mechanisms. Systemic vasodilation is often the first manifestation of the circulatory effect of liver disease. Initially, the effects of this vasodilation are counteracted through augmented cardiac output to maintain mean arterial pressure according to the following relationship:

$$MAP = \text{Cardiac Output} \times \text{Systemic Vascular Resistance}$$

Additionally, splanchnic vasodilation leads to increased levels of aldosterone leading to sodium and water retention, accentuating the hyperdynamic state [26].

The vasodilation of liver disease does not occur equally in all vascular beds, but rather represents more of a “splanchnic steal”, with progressive vasodilation of the splanchnic arteries and veins. Portal hypertension leads to endothelial stretching, shear stress, and increased vascular endothelial growth factor activity. This leads to elevated levels of nitric oxide in local vascular beds, causing vasodilation [27]. The reason for preferential splanchnic arterial and venous vasodilation is not completely understood, however it may reflect intestinal bacterial translocation leading and localized endotoxin release [28]. This activates a neurohumoral reflex, which precipitates peripheral vasoconstriction to maintain systemic vascular resistance, ultimately leading to reduced tissue perfusion [29].

Additionally liver failure is associated with a sepsis-like physiology, with bacterial translocation, endotoxin, and alterations in the concentrations of inflammatory mediators such as TNF- $\alpha$ , IL-1, and IL-6. Mediators of this sepsis like state include nitric oxide, adenosine, tachykinins, and calcitonin-gene-related peptide [30]. This systemic inflammatory response is observed in the majority of patients with acute liver failure including a sizeable portion of patients that that did not become infected [31].

The relative immunodeficiency in patients with liver failure also confers a propensity for infection and sepsis. Reasons for the sepsis-like state include severely decreased TNF- $\alpha$  production and HLA-DR expression [32]. Additionally, Kupffer cell dysfunction can decrease cell-mediated immunity, leading to a relative immune deficiency and further potentiation of the vasodilated state of liver failure [33].

When this vasodilated, hyperdynamic state is compensated, mean arterial pressure and thus cerebral perfusion pressure is maintained. However, during acute exacerbations and critical illness, systemic blood pressure can fall precipitously and ultimately worsen cerebral perfusion pressure.



## 6.6 Respiratory Effect on Cerebrovascular Physiology in Liver Failure

Liver disease can be associated with respiratory failure from a variety of mechanisms. These can include acute respiratory distress, volume overload, ventilation/perfusion mismatching, sepsis, aspiration, and intrapulmonary shunting. Hypoxemia is almost universally observed. Hypercapnea is common, which clinically can both mask and worsen underlying encephalopathy as well as cerebral edema.

### 6.6.1 Role of Hypoxia on Cerebral Circulation

The brain consumes a high percentage of the body's oxygen content; decreases in arterial oxygen content impact blood flow, through a nitric oxide mediated mechanism [34]. This mechanism is likely dominated by local effects, in which local hypoxia induces a drop in ATP which opens potassium channels on smooth muscle, therefore leading to hyperpolarization and vasodilation [35].

This vasodilation is dependent on the relative degree of hypoxia [36].  $\text{PaO}_2$  levels  $<50$  mmHg induce up to a fourfold increase in cerebral blood flow [36]. The hypoxia mediated vasodilation mechanism has also been implicated as the dominant mechanism for the vasodilation observed in both hypotension and seizures [16].

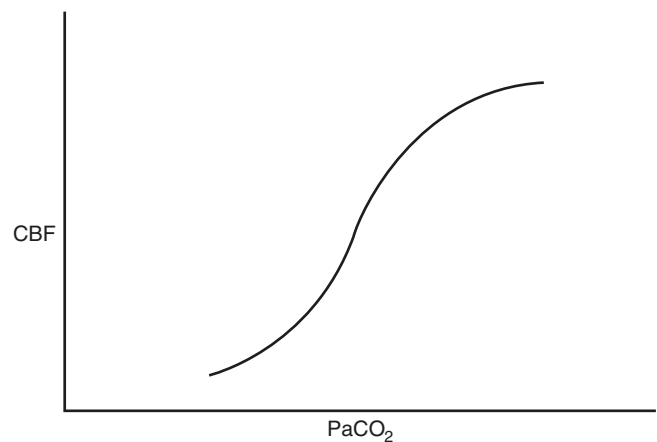
### 6.6.2 Effect of Hyperoxia on Cerebral Circulation

Since cerebral blood flow inversely correlates with  $\text{FiO}_2$ , hyperoxia may slightly decrease cerebral blood flow in a concentration-dependent manner. Although not well studied in acute liver failure, this has been demonstrated in similar populations, both in healthy, young adults [37], as well as in patients with severe head injury [38]. Additionally, both hyperoxia and hypoxia alter cerebral oxygen metabolism in a concentration-dependent manner [39].

To optimize both cerebral oxygen delivery as well as blood flow in both chronic and acute liver failure, normoxia should be the target, with a  $\text{PaO}_2$  of 80–120 mmHg.

### 6.6.3 Role of Hypercarbia on Cerebral Circulation

The role of hypercarbia on cerebral blood flow is well described. Increases in the arterial  $\text{CO}_2$  concentration lowers the pH, which causes a profound and reversible dilation of cerebral blood vessels and concomitantly an increase in cerebral blood flow. This relationship has been modeled and can likely be predicted in a sigmoid fashion (Fig. 6.2) [40].



**Fig. 6.2** Relationship of arterial carbon dioxide ( $\text{PaCO}_2$ ) and cerebral blood flow (CBF)

Both cerebral blood volume and flow increase with intracranial acidosis; however, the increase in cerebral blood flow was greater than the increase in cerebral blood volume, suggesting that an increase in vascular blood velocity also occurs [41]. Although the mechanism is not completely understood, it is likely related to the effect of extracellular hydrogen ions on vascular smooth muscle.

As with oxygen levels, normocarbica is likely ideal, avoiding the effects of decreased CPP due to vasodilation in the setting of hypercapnea, along with the decreased  $\text{O}_2$  delivery, which can be seen in hypocapnea.

## 6.7 Cerebrovascular Changes in Acute Liver Failure

### 6.7.1 Definition and Epidemiology

Acute liver failure produces a spectrum of clinical manifestations characterized by acute liver injury, severe hepatocellular dysfunction, and hepatic encephalopathy. Around 2000 people develop acute liver failure annually, with a high mortality. The poor prognosis is related to the multi-organ failure that follows the loss of hepatocyte function.

Cerebral manifestations are an important part of the constellation of symptoms that accompany acute liver failure, and comprise the defining clinical feature that separates acute hepatic failure from severe acute hepatitis. These manifestations include hepatic encephalopathy (discussed below) and cerebral edema.

### 6.7.2 Pathophysiology of Cerebral Edema in Acute Liver Failure

The essential cerebrovascular derangement in acute liver failure is the same as that observed in traumatic brain injury,

encephalitis, cerebral ischemia, or malignancy: a decrease in cerebral perfusion pressure. However, there are several unique pathophysiologic manifestations of acute hepatic failure. Although the mechanisms for the cerebral edema of acute liver failure are not completely understood, they likely include cerebral hyperemia, elevated glutamate levels, effects of elevated ammonia, astrocytic swelling, cytotoxic brain edema, osmotic stress, and breakdown of the blood brain barrier [42].

### 6.7.3 Alterations of Blood Brain Barrier Permeability

The blood brain barrier is composed of endothelial cells lining the cerebral microvessels to form the neurovascular unit [43]. The components include endothelial cells, astrocyte end-feet, and pericytes. Tight junctions, which maintain the integrity of this barrier and impede the influx of most compounds from entering the brain, break down in acute liver failure [44].

### 6.7.4 Toxic Effect of Ammonia and Osmotic Derangements Leading to Edema

The breakdown of the blood brain barrier allows for the introduction and buildup of several toxic substances such as ammonia, glutamine, and alanine. These contribute to the swelling of cortical astrocytes, which represents the central neuropathologic abnormality in the cerebral edema of acute liver failure [45]. The mechanisms of astrocyte swelling due to ammonia include oxidative stress, elevated transcription factors, and signaling kinases. Elevated inflammation signaled by levels of TNF- $\alpha$  was also associated with higher cerebral blood flow and ultimately intracranial pressure [46].

The concomitant inflammation that results from the accumulation of ammonia, glutamate, and other amino acids contributes to an osmotic derangement in astrocytes [47], mediated by an impact on sodium, potassium, and chloride transporters as well as aquaporin-4, allowing for an altered water homeostasis and astrocyte swelling [48].

### 6.7.5 Clinical Impact of Cerebral Swelling in Acute Liver Failure

The clinical impact of these pathophysiologic changes is a brain prone to edema even in the absence of high intracranial pressures. Risk factors identified include an ammonia level >150–200  $\mu\text{mol/L}$ , grade III or grade IV encephalopathy, requirement for vasopressors, and infection. These changes occur in acute liver failure rather than in chronic liver failure because the acuity of the changes leads to cerebral hyperemia matched with reduced cerebral metabolic rate to result in hepatic coma.

### 6.7.6 Monitoring Cerebrovascular Changes in Acute Liver Failure

Cerebral edema accounts for a significant proportion of morbidity and mortality in acute liver failure, and thus should be carefully considered in any patient with acute liver failure and altered mental status. Clinical monitoring for manifestations of cerebral edema should be regularly performed. These include observation for hyperventilation, hemodynamic lability, pupil asymmetry or symmetric dilation, posturing (either flexor or extensor), seizure activity, or bradyarrhythmias (seen late in the course).

Other forms of monitoring are frequently performed to identify and potentially manage cases of intracranial hypertension. These include invasive neuromonitoring, transcranial Doppler ultrasound, and jugular venous oxygen saturation monitoring.

### 6.7.7 Invasive Neuromonitoring

Invasive monitoring involves placement of a catheter within the cranial vault to monitor and potentially manage elevated intracranial pressures. This can come in the form of a ventriculostomy or an intraparenchymal fiberoptic catheter.

Variability exists in the precision and safety of various devices [49]. While invasive monitoring allows for more direct measurement of the intracranial pressure and more aggressive management of intracranial hypertension [50], there are potential drawbacks, especially in the setting of liver disease with the associated coagulopathy and propensity for infection. Overall, placement of these catheters may not be associated with improved outcomes [51].

### 6.7.8 Transcranial Doppler Measurement

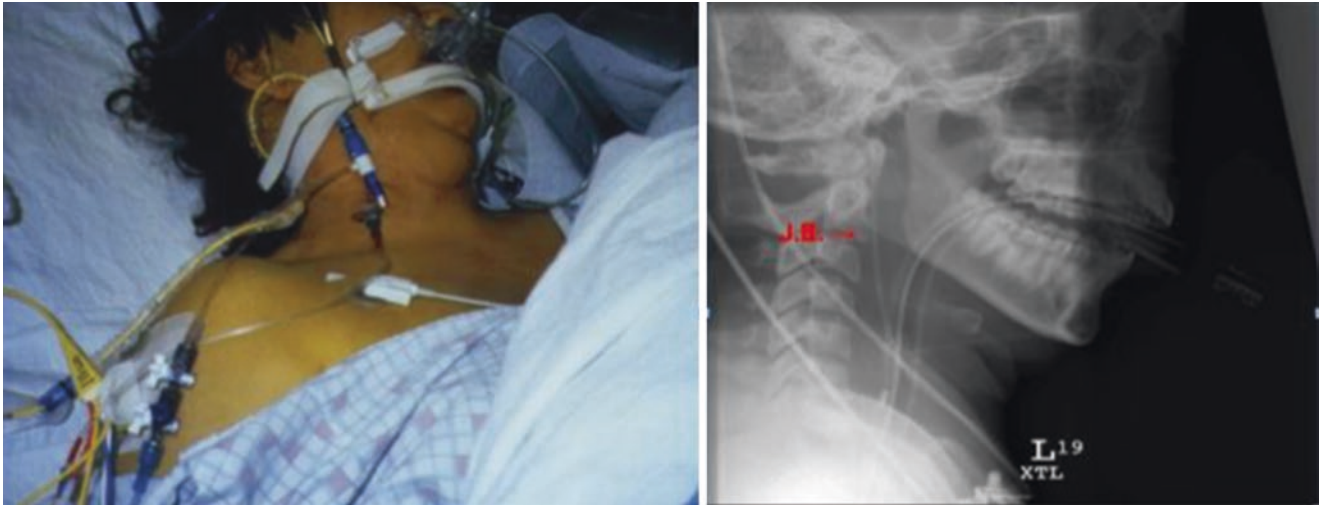
Serial transcranial Doppler ultrasound measurements can be used to detect cerebral blood flow velocity as a marker of early cerebral hyperperfusion or hypoperfusion. Transcranial Doppler velocity measurements assume that cerebral blood flow can be estimated with the following equation:

$$\text{Flow} = \text{Velocity} \times \text{Area}$$

Therefore, at a constant vessel resistance, changes in blood flow are proportionate to changes in velocity.

### 6.7.9 Jugular Venous Monitoring

Cerebral blood flow can also be estimated as a proportion of the cerebral oxygen consumption to the oxygen



**Fig. 6.3** Jugular bulb catheter

delivered. This can be estimated from the Kety-Schmidt relationship, which depends on intact metabolic autoregulation:

$$\text{Cerebral Blood Flow} = \frac{\text{Cerebral Metabolic Rate}}{\text{O}_2\text{arterial} - \text{O}_2\text{venous}}$$

In acute liver failure, especially in cases of hepatic coma, the cerebral metabolic rate is constant and low. Therefore it follows that cerebral blood flow can be estimated according to the following relationship:

$$\text{Cerebral Blood Flow} = \frac{1}{\text{O}_2\text{art} - \text{O}_2\text{ven}}$$

Assuming normal arterial oxygen saturation, the oxygen saturation of the blood in the internal jugular vein can serve as a surrogate for cerebral blood flow. Jugular oxygen saturation can be measured in a jugular bulb catheter placed retrograde into the internal jugular vein (Fig. 6.3).

However, the Kety-Schmidt estimate of cerebral blood flow also depends upon the ability of delivered oxygen to reach the mitochondria, and on the ability of the mitochondria to utilize that oxygen. In settings of cerebral edema, the diffusion of oxygen may be impaired, and in many acute CNS disorders, the mitochondria are dysfunctional and unable to utilize oxygen for aerobic metabolism. As a consequence, a narrowed gradient between arterial oxygen content and jugular venous oxygen content may not reflect an increase in cerebral blood flow, but rather an inability to metabolize the oxygen delivered. Hence, one should not assume that hyperventilation can be used safely to lower intracranial pressure based on an apparently elevated jugular venous oxygen content (or saturation).

## 6.8 Acute on Chronic Liver Failure (ACLF)

Acute on Chronic Liver Failure (ACLF) is a clinical syndrome characterized by acute and severe hepatic abnormalities resulting from precipitating events in patients with underlying chronic liver disease (CLD). ACLF differs from decompensated liver cirrhosis by the presence of extrahepatic organ failure(s) and by a high short-term mortality resembling that of Acute Liver Failure (ALF).

### 6.8.1 Heterogeneity of Definitions

Due to the relatively recent recognition of ACLF as an entity distinct from decompensated cirrhosis and ALF, the key terms ‘acute’, ‘chronic’, and ‘organ failure’ have several variations, resulting in several definitions of ACLF reported in a recent systematic review [52]. All available definitions emphasize three common points: 1) presence of CLD; 2) rapid yet theoretically reversible deterioration of liver function; and 3) high short-term mortality [53]. The lack of a universally accepted definition is problematic in both timely identification of patients and necessary therapeutic trials to improve outcome.

Currently, two major consensus definitions are widely used (Table 6.2). The ‘Eastern’ definition of ACLF, proposed by the Asian Pacific Association for the Study of the Liver (APASL), focuses exclusively on liver failure [54, 55]. The ‘Western’ definition of ACLF, proposed by the American Association for the Study of the Liver Disease (AASLD)/European Association for the Study of the Liver (EASL) consortium, includes concurrent extrahepatic organ failure [56, 57]. Both definitions now include a high 4-week mortality. An accurate prevalence of ACLF is difficult to determine due to the heterogeneous definition of

**Table 6.2** The similarities and differences in western and eastern definition of ACLF

APASL-ACLF	EASL and AASLD-ACLF
<b>Definition</b>	
Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease associated with a high 4-week mortality	An acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 4 weeks due to multisystem organ failure
<b>Differences</b>	
Acute insult or precipitant should be hepatic only	Acute insult or precipitant can be hepatic or extrahepatic
Variceal bleeding, only if it results in liver failure is considered a precipitant	Variceal bleeding is considered a precipitant leading to ACLF
Sepsis is a complication of liver failure, persistent inflammation, SIRS and CARS, which leads to immune paresis, hence diagnosis of ACLF is made early with potential of recovery	Sepsis as a primary precipitant leading to ACLF, hence diagnosis of ACLF is delayed with little potential for recovery of organ failure (s)
Duration between acute insult and development of ACLF is 4 weeks	No duration specified
CLD includes patients with and without cirrhosis, but not those with decompensated cirrhosis	CLD includes those with (ACLF type B & C) and without (ACLF type A) cirrhosis with or without prior decompensation
A defined cut-off for liver failure; both jaundice (bilirubin >85 $\mu$ mol/L) and coagulopathy (INR >1.5 or prothrombin activity of <40%)	No defined cut-off for liver failure. Defined by organ failure cut-off values in CLIF-SOFA score. Either bilirubin or INR levels can independently define liver failure
Disease severity score not defined	Disease severity score not defined, but indirectly interpreted through organ failure scores, as CLIF-SOFA score and represent both hepatic and nonhepatic ACLF
<b>Similarities</b>	
<ul style="list-style-type: none"> <li>• ACLF defined as a distinct entity that is different from ALF</li> <li>• Duration showing high mortality at 4 weeks</li> <li>• Needs early consideration of liver transplant</li> <li>• Organ failure and sepsis are the most common cause of high mortality</li> </ul>	

Adapted from Sarin SK et al. [63]

Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2016;13:131–49. *AASLD* American Association for the Study of Liver Disease, *ACLF* acute-on-chronic liver failure, *ALF* acute liver failure, *APASL* Asian Pacific Association for the Study of the Liver, *CARS* compensatory anti-inflammatory response syndrome, *CLD* chronic liver disease, *CLIF* chronic liver failure, *EASL* European Association for the Study of the Liver, *SIRS* systematic inflammatory response syndrome, *SOFA* sequential organ failure assessment

CLD. Nevertheless, based on registry data, ACLF is estimated to occur in 24–40% of hospitalized patients with cirrhosis [56, 58–62].

Two prospective, observational studies were conducted to better classify hospitalized patients with cirrhosis: 1) The EASL-Chronic Liver Failure (CLIF) Consortium Acute on Chronic Liver Failure in Cirrhosis (CANONIC) [56]; and 2) the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) [58]. NACSELD investigators focused on hospitalized cirrhotic patients with infection, with a goal to develop simple bedside clinical criteria to accurately identify potential survivors for cost-effective healthcare resource utilization [58]. As a result, Infection-related ACLF (I-ACLF) was proposed, defined as two or more organ system failures in cirrhotic patients with suspected or documented infection, and predictive of poor survival. On the other hand, the CANONIC study, with the most comprehensive registry of hospitalized cirrhotic patients with acute decompensation, aimed to stratify cirrhotic patients with ACLF by short-term mortality risk. As a result, the severity of ACLF is graded into different stages according to the number of organ failures on CLIF-ACLF grade 1, 2, and 3, and mortality correlates with ACLF grade [56]. Importantly, CLIF-ACLF grades are mainly driven by kidney and brain failure, the latter defined as West-Haven grade 3 or 4 Hepatic Encephalopathy (HE). As in ALF and decompensated liver cirrhosis, HE carries an important prognostic significance in ACLF. However, HE associated with ACLF appears to be a distinct entity from HE in ALF or decompensated cirrhosis.

### 6.8.2 Brain Failure in ACLF

All three definitions used by APASL, EASL, and NACSELD recognize the brain as one of the major failing organs in ACLF and define brain failure as West-Haven HE grade 3 or 4 (Table 6.3).

Current understanding of neurological sequelae of ACLF is limited to clinical observation, however, animal models of ACLF and studies based on imaging modalities are beginning to better characterize acute events occurring in the brain. Although thought to occur only in ALF, intracranial hypertension and cerebral edema in four cirrhotic patients following emergency transjugular intrahepatic portosystemic shunt (TIPS) [65]. This was followed by a report of 12 patients presenting with acutely decompensated cirrhosis with clinical and radiographic evidence of intracranial hypertension and cerebral edema [66]. Two patients treated with liver transplantation showed clinical neurological resolution, indicating a potential therapeutic window for intervention in this often-fatal presentation. The resolution of cerebral edema was again demonstrated on MRI in ACLF patients with severe HE [67].

The frequency of brain failure in patients with ACLF has been reported to be approximately 25% in the CANONIC study and 56% in the NACSELD study [56, 58]. The brain was the most common failing organ in the NACSELD cohort. The difference in frequency of brain failure likely reflects a



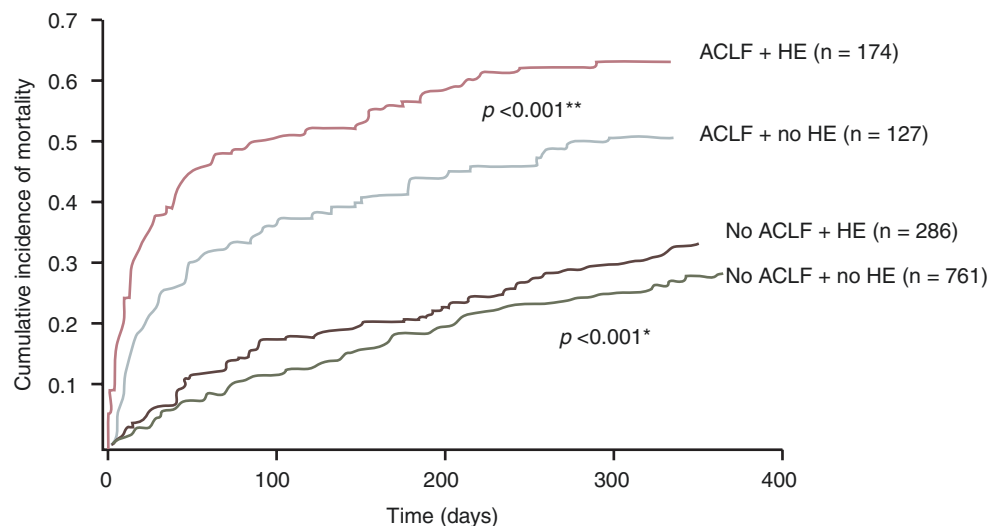
**Table 6.3** Examples of available definitions of organ failures used in patients with cirrhosis

Failing organ	Asian Pacific Association for the Study of the Liver organ failures definition [3, 4]	European Association for the Study of Liver-Chronic Liver failure organ failures definition [12]	North American Consortium for Study of End-stage Liver Disease organ failures definition [7]
Liver	Total bilirubin $\geq 5$ mg/dL and INR $\geq 1.5$	Bilirubin level of $>12$ mg/dL	–
Kidney	Acute Kidney Injury Network criteria	Creatinine level of $\geq 2.0$ mg/dL or renal replacement	Need for dialysis or other forms of renal replacement therapy
Brain	West-Haven hepatic encephalopathy grade 3–4	West-Haven hepatic encephalopathy grade 3–4	West-Haven hepatic encephalopathy grade 3–4
Coagulation	INR $\geq 1.5$	INR $\geq 2.5$	–
Circulation	–	Use of vasopressor (terlipressin and/or catecholamines)	Presence of shock defined by mean arterial pressure $<60$ mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output
Respiration	–	$PaO_2/FiO_2$ of $\leq 200$ or $SpO_2/FiO_2$ of $\leq 214$ or need for mechanical ventilation	Need for mechanical ventilation

Adapted from Hernaez et al. [64]

Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. Gut 2017;66:541–53

$FiO_2$  fraction of inspired oxygen, INR international normalised ratio,  $PaO_2$  partial pressure of arterial oxygen,  $SpO_2$  pulse oximetric saturation



**Fig. 6.4** Actuarial survival curve of hospitalized cirrhotic patients showing mortality of patients with or without ACLF in combination of with or without overt hepatic encephalopathy. Mortality rate was significantly higher in patients with ACLF and HE in comparison with non-HE patients with ACLF. In decompensated cirrhosis, HE was also related to an increased mortality. \* $p$  value comparing presence vs.

absence of HE in patients without ACLF; \*\* $p$  value comparing presence vs. absence of HE in patients with ACLF. Adapted from Cordoba J. et al. and Romero-Gomez M. et al. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol 2015;62:437–47 [68, 69]

broader inclusion of patients in the CANONIC study, compared to the NACSELD study, which was specific to infection-related ACLF. A twofold higher frequency of brain failure in infection-related ACLF compared to that in ACLF from all causes suggests that local or systemic infection plays an important role in the pathogenesis of HE in ACLF by triggering the systemic inflammatory response. The role of inflammation in HE is further discussed later in this section.

HE, independent of other extrahepatic organ failure, adds significantly to the risk of death in patients with ACLF, as shown in the CANONIC study [56] short and long term mortality in patients with HE was further modulated by age,

severity of HE, and parameters associated with liver function such as creatinine, bilirubin, INR, and sodium [68]. HE associated with ACLF appears to be distinct from isolated HE without ACLF in that it affects younger patients in the setting of exaggerated systemic inflammatory response precipitated by bacterial infection, hyponatremia, and/or alcohol use. This contrasts with isolated HE without ACLF, which occurs in older patients, often in the setting of preceding diuretic treatment [68] (Fig. 6.4). The only identified independent risk factor for the development of HE in ACLF is previous HE, supporting the view that HE is a highly recurrent disorder with much needed strategies for primary prevention.



In the NACSELD study, the crude 30-day survival rate in patients with brain failure (grade 3 or 4 HE) was significantly lower than those without brain failure although the predictive value of HE on survival independent of other organ failures has not been reported [58].

### 6.8.3 Pathophysiology of HE in ACLF

Local and systemic factors have been implicated in the pathogenesis of HE in ACLF. Hyperammonemia, acute inflammation, and changes in cerebral hemodynamics likely contribute to development and progression of HE in ACLF, however their individual relative contribution has not been clearly defined [70].

### 6.8.4 Cerebral Edema

HE associated with ACLF can rapidly progress to intracranial hypertension and cerebral edema resulting in coma and/or death, suggesting shared pathophysiology with ALF. It is controversial how often cerebral edema occurs in HE associated with ACLF. Joshi et al., using CT brain imaging, reported that cerebral edema occurs in <5% of patients admitted to a single institution for HE and ACLF [71]. However, this is likely an underestimation because 1) only patients with clinical signs concerning for structural intracranial abnormality underwent CT imaging; and 2) many cirrhotic patients with underlying brain atrophy and some degree of cerebral edema may appear normal on CT without obvious clinical manifestations of intracranial hypertension. As mentioned above, more advanced imaging techniques using magnetic resonance have demonstrated resolution of cerebral edema in ACLF after successful liver transplantation [17]. It remains unclear why in some patients with HE and ACLF severe neurological sequelae of cerebral edema and intracranial hypertension ensue. One can postulate that individual brain 'resilience' against acute pathological challenge in ACLF (e.g. bacterial infection, SIRS, etc.) is determined by many factors, including chronic pathologic changes (e.g. astrocytic dysfunction, low-grade cerebral inflammatory milieu, and impaired cerebrovascular autoregulation) and acute severity of multi organ system failure leading to overwhelming inflammatory response.

As in ALF, ammonia is likely to play a role in accumulation of water in the astrocytes of patients with ACLF, via impaired glutamate-glutamine cycling and increased oxidative stress among other postulated mechanisms. Hyponatremia, a common finding in ACLF, may exacerbate astrocyte swelling due to osmolality differences between the intracellular and extracellular compartments [72]. While the

relationship between hyponatremia and presence of cerebral edema in patients with ACLF has not been systemically examined, hyponatremia further increases mortality in patients with HE associated with ACLF [68].

### 6.8.5 Altered Cerebral Hemodynamics

Patients with ACLF are frequently in circulatory failure, defined by reduced mean arterial pressure [56]. Normally, cerebral blood flow is kept constant within a wide range of mean arterial blood pressure values (cerebral autoregulation), via reactive dilatation or constriction of cerebral resistance vessels. Impaired cerebral autoregulation in ALF has been demonstrated using noninvasive transcranial Doppler sonography (TCD) where reduced vertebral blood flow and increased vascular indices likely contribute to cerebral edema and intracranial hypertension [73–75]. Similarly, Kawakami and colleagues reported the TCD finding of an abnormally elevated pulsatility index in a patient with ACLF and Grade 3 HE, reflecting increased intracranial pressure [76]. Further studies are necessary to better understand cerebral hemodynamics in patients with ACLF, specifically with regard to development and progression of cerebral edema and HE.

### 6.8.6 Systemic Inflammation

Systemic inflammation is a hallmark of ACLF, with or without identified infection [56, 77]. In the CANONIC cohort, pro-inflammatory cytokines including interleukin (IL)-6 and IL-8 are higher in hospitalized cirrhotic patients with ACLF than in those without [78]. Plasma concentrations of IL-6 and IL-8 were associated with the severity of ACLF and with short-term mortality. In a smaller cohort of 55 cirrhotic patients (26 with ACLF), significant changes in plasma cytokine patterns were observed from healthy controls to patients without ACLF, which was further exaggerated in patients with ACLF. Altered cytokines in ACLF, including increased level of vascular cell adhesion molecule 1 (VCAM-1) and decreased level of granulocyte-macrophage colony-stimulating factor (GM-CSF), are functionally related to monocyte/macrophage immune response and correlated with increased 3-month mortality [79]. Another study showed increased levels of prostaglandin E2 (PGE2) in plasma from patients with ACLF, which may suppress macrophage pro-inflammatory cytokine secretion and bacterial killing [80]. Taken together, these findings suggest that marked systemic inflammation, impaired innate immune response, and some degree of immune suppression play a role in the pathophysiology of ACLF, resulting in organ failure and hemodynamic col-

lapse similar to sepsis. In one study, bacterial infection mostly due to spontaneous bacterial peritonitis is identified in approximately 30% of patients with ACLF. Severe alcoholic hepatitis and systemic inflammation were identified in 25% and 45% respectively.

### 6.8.7 Synergism: Hyperammonemia and Inflammation

Despite the widely accepted pathogenic importance of ammonia in HE, data confirming a direct correlation between the absolute concentration of ammonia and the severity of HE are limited. While plasma ammonia concentrations in patients with ACLF and severe HE were higher than those with decompensated cirrhosis and severe HE [71], ammonia concentrations were poorly correlated with advancing HE [70]. In the same study, the presence and severity of Systemic Inflammatory Response Syndrome (SIRS) was correlated with severe HE in ACLF [70]. In a study of ten hospitalized cirrhotic patients with clinical evidence of infection, induced hyperammonemia using oral administration of an amino-acid solution resulted in significant worsening of neuropsychological scores during the state of SIRS, but not after its resolution; this finding suggests synergy between systemic inflammation and hyperammonemia in the pathogenesis of HE [81].

## 6.9 Management of Hepatic Encephalopathy and Cerebral Edema

Although the recommendations below are aimed at patients with ALF, one can make a reasonable argument to use the same intervention in patients with ACLF.

The treatment is directed at limiting gut ammonia production and the avoidance of aggravating factors such as infection, ileus, obstipation, gastrointestinal hemorrhage, and other CNS depressants. Endotracheal intubation for grade III and IV hepatic encephalopathy is usually indicated. Lactulose may be useful in the treatment of patients with grade I or II encephalopathy; however, administration of lactulose does not improve survival in advanced encephalopathy. The efficacy of lactulose in ALF has not been tested in clinical trials. This agent should be used with caution because of the risk of hypernatremia, dehydration due to diarrhea, potential for bowel distension to disrupt the surgical field and ileus. Lactulose by enema (300 g in 700 mL saline every 4–6 h) remains an option in patients who are unable to tolerate oral or nasogastric administration.

Oral metronidazole, neomycin, and rifaximin directed against ammonia-producing gut flora have been employed. However, metronidazole may be neurotoxic in hepatic

failure; and neomycin, although minimally absorbed, can still cause nephrotoxicity and ototoxicity. Rifaximin is effective in decreasing ammonia due to hepatic encephalopathy with good evidence for its use in chronic liver failure and should be considered as an adjunct to lactulose in treating encephalopathy due to ammonia due to ALF. Endogenous benzodiazepine-like substances have been identified in the cerebrospinal fluid of patients with hepatic encephalopathy. Flumazenil, a benzodiazepine receptor antagonist, has been used (0.2–20 mg) with some success to provide short-term improvement in patients with hepatic encephalopathy. Administration of L-ornithine-L-aspartate (LOLA) in patients with ALF was ineffective in reducing circulating ammonia levels or improving survival and may cause increased seizure activity. L-Ornithine phenylacetate remains a potential temporary agent for treatment of hepatic encephalopathy while awaiting transplant, however has yet to be validated in humans.

Management of cerebral edema requires maintaining the delicate balance between mean arterial pressure (MAP) and ICP to preserve adequate cerebral perfusion (Table 6.4).

**Table 6.4** Preventive and therapeutic intervention for patients with cerebral edema and intracranial hypertension (adapted from DellaVolpe et al., text book of critical care) [82]

General measures
Head of bed elevation to 30-degree angle, and maintain patient's neck in neutral position.
Endotracheal intubation for grade III or IV hepatic encephalopathy
Minimize tactile and tracheal stimulation, including airway suctioning.
Avoid hypovolemia and hypervolemia.
Avoid hypertension.
Avoid hypercapnia and hypoxemia.
Monitor and maintain ICP < 15 mmHg.
Maintain CPP > 50 mmHg.
Monitor and maintain SvjO <sub>2</sub> between 55% and 85%.
Use serial transcranial Doppler monitoring to titrate therapy.
Management of intracranial hypertension
Mannitol boluses, 0.5–1.0 g/kg body weight
Hyperventilation titrated to a Pco <sub>2</sub> of 28–30 mmHg
Induced moderate hypothermia to 32–33 °C
Achieve serum sodium levels of 145–155 mEq/L.
Induced coma with propofol or pentobarbital titrated to burst suppression of 5–10 cycles/s
CVVH for oliguria and hyperosmolarity (>310 mOsm/L)
Other unproven therapies
Prophylactic phenytoin
Indomethacin, 25 mg intravenous bolus
Plasmapheresis with
Total hepatectomy as a bridge to transplant

CPP cerebral perfusion pressure, CVVH continuous venovenous hemofiltration, ICP intracranial pressure, SvjO<sub>2</sub> jugular bulb oxygen saturation

## References

- Cipolla MJ. Control of cerebral blood flow. San Rafael, CA: Morgan & Claypool Life Sciences; 2009.
- Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Ann Neurol*. 1994;36(4):557–65.
- Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev*. 2005;57(2):173–85.
- Drake CT, Iadecola C. The role of neuronal signaling in controlling cerebral blood flow. *Brain Lang*. 2007;102(2):141–52.
- Ngai AC, Ko KR, Morii SE, Winn HR. Effect of sciatic nerve stimulation on pial arterioles in rats. *Am J Physiol Heart Circ Physiol*. 1988;254(1):H133–9.
- Cox SB, Woolsey TA, Rovainen CM. Localized dynamic changes in cortical blood flow with whisker stimulation corresponds to matched vascular and neuronal architecture of rat barrels. *J Cereb Blood Flow Metab*. 1993;13(6):899–913.
- Rusakov DA. Disentangling calcium-driven astrocyte physiology. *Nat Rev Neurosci*. 2015;16(4):226–33.
- Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. *Nat Neurosci*. 2007;10(11):1369–76.
- Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res*. 1990;66(1):8–17.
- Lou HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr*. 1979;94(1):118–21.
- Yazici B, Erdogmus B, Tugay A. Cerebral blood flow measurements of the extracranial carotid and vertebral arteries with Doppler ultrasonography in healthy adults. *Diagn Interv Radiol*. 2005;11(4):195.
- Panerai RB. Cerebral autoregulation: from models to clinical applications. *Cardiovasc Eng*. 2008;8(1):42–59.
- Osol GE, Halpern WI. Myogenic properties of cerebral blood vessels from normotensive and hypertensive rats. *Am J Physiol Heart Circ Physiol*. 1985;249(5):H914–21.
- Kontos HA, Wei EP. Oxygen-dependent mechanisms in cerebral autoregulation. *Ann Biomed Eng*. 1985;13(3-4):329–34.
- Paternò R, Heistad DD, Faraci FM. Potassium channels modulate cerebral autoregulation during acute hypertension. *Am J Physiol Heart Circ Physiol*. 2000;278(6):H2003–7.
- Kontos HA, Wei EP, Raper AJ, Rosenblum WI, Navari RM, Patterson JL. Role of tissue hypoxia in local regulation of cerebral microcirculation. *Am J Physiol Heart Circ Physiol*. 1978;234(5):H582–91.
- Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med*. 2007;146(1):34–44.
- Faraci FM, Heistad DD. Regulation of the cerebral circulation: role of endothelium and potassium channels. *Physiol Rev*. 1998;78(1):53–97.
- Meyer JS, Waltz AG, Coto F. Pathogenesis of cerebral vasospasm in hypertensive encephalopathy I. Effects of acute increases in intraluminal blood pressure on pial blood flow. *Neurology*. 1960;10(8):735.
- Skinhøj E, Strandgaard S. Pathogenesis of hypertensive encephalopathy. *Lancet*. 1973;301(7801):461–2.
- Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. *Hypertension*. 2007;49(5):977–8.
- Prabhu R, Srinivasan R, Jayanthi V. Prevalence of arterial hypertension in cirrhosis of liver. *Saudi J Gastroenterol*. 2009;15(1):65.
- Henriksen JH, Moller S. Liver cirrhosis and arterial hypertension. *World J Gastroenterol*. 2006;12(5):678.
- Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525–34.
- Wagener G, Kovalevskaya G, Minhaz M, Mattis F, Emond JC, Landry DW. Vasopressin deficiency and vasodilatory state in end-stage liver disease. *J Cardiothorac Vasc Anesth*. 2011;25(4):665–70.
- Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology*. 1988;8(5):1151–7.
- Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology*. 2006;43(S1):S121.
- La Villa G, Gentilini P. Hemodynamic alterations in liver cirrhosis. *Mol Aspects Med*. 2008;29(1):112–8.
- Newby DE, Hayes PC. Hyperdynamic circulation in liver cirrhosis: not peripheral vasodilatation but ‘splanchnic steal’. *QJM*. 2002;95(12):827–30.
- Ginès P, Fernández-Esparrach G, Arroyo V. 10 Ascites and renal functional abnormalities in cirrhosis. Pathogenesis and treatment. *Baillieres Clin Gastroenterol*. 1997;11(2):365–85.
- Rolando N, Wade JJ, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology*. 2000;32(4):734–9.
- Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, Bach J, Geier A, Purucker EA, Gressner AM, Matern S. Patients with acute on chronic liver failure display ‘sepsis-like’ immune paralysis. *J Hepatol*. 2005;42(2):195–201.
- Bilzer M, Roggel F, Gerbes AL. Role of Kupffer cells in host defense and liver disease. *Liver Int*. 2006;26(10):1175–86.
- Van Mil AH, Spilt A, Van Buchem MA, Bollen EL, Teppema L, Westendorp RG, Blauw GJ. Nitric oxide mediates hypoxia-induced cerebral vasodilation in humans. *J Appl Physiol*. 2002;92(3):962–6.
- Johnston AJ, Steiner LA, Gupta AK, Menon DK. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. *Br J Anaesth*. 2003;90(6):774–86.
- Wei EP, Randad RS, Levasseur JE, Abraham DJ, Kontos HA. Effect of local change in O<sub>2</sub> saturation of hemoglobin on cerebral vasodilation from hypoxia and hypotension. *Am J Physiol Heart Circ Physiol*. 1993;265(4):H1439–43.
- Watson NA, Beards SC, Altaf N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. *Eur J Anaesthesiol*. 2000;17(3):152–9.
- Menzel M, Döppner EM, Zauner A, Soukup J, Reinert MM, Clausen T, Brockenbrough PB, Bullock R. Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism, and intracranial pressure. *J Neurosurg Anesthesiol*. 1999;11(4):240–51.
- Xu F, Liu P, Pascual JM, Xiao G, Lu H. Effect of hypoxia and hyperoxia on cerebral blood flow, blood oxygenation, and oxidative metabolism. *J Cereb Blood Flow Metab*. 2012;32(10):1909–18.
- Duong TQ, Iadecola C, Kim SG. Effect of hyperoxia, hypercapnia, and hypoxia on cerebral interstitial oxygen tension and cerebral blood flow. *Magn Reson Med*. 2001;45(1):61–70.
- Ito H, Kanno I, Ibaraki M, Hatazawa J, Miura S. Changes in human cerebral blood flow and cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. *J Cereb Blood Flow Metab*. 2003;23(6):665–70.
- Blei AT. Brain edema in acute liver failure. *Crit Care Clin*. 2008;24(1):99–114.
- Abbott NJ, Rönnbäck L, Hansson E. Astrocyte–endothelial interactions at the blood–brain barrier. *Nat Rev Neurosci*. 2006;7(1):41–53.
- Ballabh P, Braun A, Nedergaard M. The blood–brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol Dis*. 2004;16(1):1–3.
- Swain M, Butterworth RF, Blei AT. Ammonia and related amino acids in the pathogenesis of brain edema in acute ischemic liver failure in rats. *Hepatology*. 1992;15(3):449–53.
- Jalan R, Damink SW, Hayes PC, Deutz NE, Lee A. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. *J Hepatol*. 2004;41(4):613–20.

47. Blei AT. The pathophysiology of brain edema in acute liver failure. *Neurochem Int.* 2005;47(1):71–7.
48. Rao KV, Jayakumar AR, Norenberg MD. Brain edema in acute liver failure. *Metab Brain Dis.* 2014;29(4):927–36.
49. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet.* 1993;341(8838):157–8.
50. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, Han S, Harrison ME, Stravitz TR, Munoz S, Brown R. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl.* 2005;11(12):1581–9.
51. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. *Crit Care Med.* 2014;42(5):1157.
52. Wlodzimierz KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. *Liver Int.* 2013;33:40–52.
53. Amathieu R, Al-khafaji A. Definitions-of-Acute-On-Chronic-Liver-Failure-The-Past-the-Present-and-the-Future. *EMJ Hepatol.* 2015;3:35–40.
54. Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatol Int.* 2014;8:453–71.
55. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int.* 2009;3:269–82.
56. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144:1426–37.e9.
57. Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an Improved Definition of Acute-on-Chronic Liver Failure. *Gastroenterology.* 2014;147:4–10.
58. Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology.* 2014;60:250–6.
59. Escorsell Mañosa À, Mas OA. Acute on chronic liver failure. *Gastroenterol Hepatol.* 2010;33:126–34.
60. Sargenti K, Prytz H, Nilsson E, Kalaitzakis E. Predictors of mortality among patients with compensated and decompensated liver cirrhosis: the role of bacterial infections and infection-related acute-on-chronic liver failure. *Scand J Gastroenterol.* 2015;50:875–83.
61. Shi Y, Yang Y, Hu Y, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. *Hepatology.* 2015;62:232–42.
62. Li H, Chen L-Y, N-n Z, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. *Sci Rep.* 2016;6:25487.
63. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol.* 2016;13:131–49.
64. Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. *Gut.* 2017;66:541–53.
65. Jalan R, Dabos K, Redhead DN, Lee A, Hayes PC. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol.* 1997;27:928–33.
66. Donovan JP, Schafer DF, Shaw BW, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. *Lancet.* 1998;351:719–21.
67. García Martínez R, Rovira A, Alonso J, et al. A long-term study of changes in the volume of brain ventricles and white matter lesions after successful liver transplantation. *Transplantation.* 2010;89:589–94.
68. Cordoba J, Ventura-Cots M, Simon-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). *J Hepatol.* 2014;60:275–81.
69. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *J Hepatol.* 2015;62:437–47.
70. Shawcross DL, Sharifi Y, Canavan JB, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. *J Hepatol.* 2011;54:640–9.
71. Joshi D, O'Grady J, Patel A, et al. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. *Liver Int.* 2014;34:362–6.
72. Córdoba J, García-Martínez R, Simón-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. *Metab Brain Dis.* 2010;25:73–80.
73. Strauss G, Hansen BA, Kirkegaard P, Rasmussen A, Hjortrup A, Larsen FS. Liver function, cerebral blood flow autoregulation, and hepatic encephalopathy in fulminant hepatic failure. *Hepatology.* 1997;25:837–9.
74. Larsen FS, Ejlersen E, Hansen BA, Knudsen GM, Tygstrup N, Secher NH. Functional loss of cerebral blood flow autoregulation in patients with fulminant hepatic failure. *J Hepatol.* 1995;23:212–7.
75. Abdo A, López O, Fernández A, et al. Transcranial Doppler sonography in fulminant hepatic failure. *Transplant Proc.* 2003;35:1859–60.
76. Kawakami M, Koda M, Murawaki Y. Cerebral pulsatility index by transcranial Doppler sonography predicts the prognosis of patients with fulminant hepatic failure. *Clin Imaging.* 2010;34:327–31.
77. Bernsmeier C, Pop OT, Singanayagam A, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. *Gastroenterology.* 2015;148:603–15.e14.
78. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology.* 2016;64:1249–64.
79. Sole C, Sola E, Morales-Ruiz M, et al. Characterization of Inflammatory Response in Acute-on-Chronic Liver Failure and Relationship with Prognosis. *Sci Rep.* 2016;6:32341.
80. O'Brien AJ, Fullerton JN, Massey KA, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. *Nat Med.* 2014;20:518–23.
81. Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J Hepatol.* 2004;40:247–54.
82. DellaVolpe J, Amatheu R, Al-Khafaji A. Fulminant hepatic failure. In: Vincent JL, Abraham E, Kochanek P, Moore FA, Fink MP, editors. *Textbook of critical care.* 7th ed. Amsterdam: Elsevier; 2016.

---

## **Part II**

# **Manifestations of Problems and Management of the Critically Ill Patient with Liver Disease**



Jody C. Olson and Patrick S. Kamath

## Abstract

Patients presenting to the intensive care unit with liver failure may be categorized into two main subtypes, those with acute liver failure and those with complications of chronic liver diseases, the former being a rare condition and the latter far more common. In both categories, patients presenting with liver failure have phenotypical features of multi-system failure, a deranged inflammatory response, and pose unique challenges for management in the intensive care unit. Differentiating acute liver failure from the liver failure associated with chronic liver disease is of critical diagnostic importance, as management strategies are distinctly different. The purpose of this chapter is to review the definitions of liver failure, the epidemiology of liver disease, and current tools to aid in prognosis of liver failure.

## Keywords

Cirrhosis • Acute-on-chronic liver failure • acute liver failure • MELD

## 7.1 Introduction

Patients presenting to the intensive care unit with liver failure may be categorized into two main subtypes, those with acute liver failure and those with complications of chronic liver diseases, the former being a rare condition and the latter far more common. In both categories, patients presenting with liver failure have phenotypical features of multi-system failure, a deranged inflammatory response, and pose unique challenges for management in the intensive care unit. Differentiating acute liver failure from the liver failure associated with chronic liver disease is of critical diagnostic importance, as management strategies are distinctly different.

Acute liver failure is a rapidly progressive condition with a potential for complete recovery, whereas the natural history of cirrhosis is that of a progressive disease resulting in eventual “end-stage” liver failure, which in absence of liver transplantation, is often fatal. In contrast to the natural history of cirrhosis, acute-on-chronic liver failure is a distinct clinical entity which results in acute deterioration of previously compensated chronic liver disease and carries high short term mortality; however it is potentially reversible and may respond to aggressive critical care support.

The purpose of this chapter is to review the terminology associated with liver failure and review the epidemiology of both acute and chronic liver disease. The use of standard language when discussing patients with liver failure aids in clear communication among healthcare providers and with patients regarding disease course and prognosis.

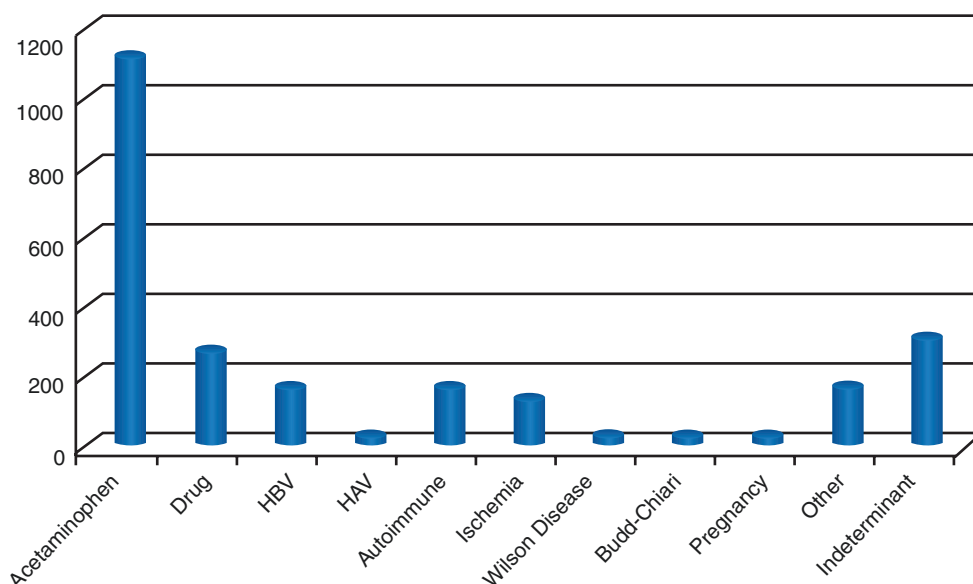
J.C. Olson, M.D., F.A.C.P. (✉)  
Hepatology and Critical Care Medicine, University of Kansas  
Medical Center, 3901 Rainbow Blvd., MS 1023, Kansas City,  
KS 66160, USA  
e-mail: [jolson2@kumc.edu](mailto:jolson2@kumc.edu)

P.S. Kamath, M.D.  
Mayo Clinic, Mayo 9 West, 200 1st St NW, Rochester,  
MN 55901, USA

## 7.2 Acute Liver Failure

Acute liver failure (ALF) is defined as hepatic encephalopathy (any grade using West Haven Criteria) with coagulopathy (International Normalized Ratio  $\geq 1.5$ ) in the setting of

**Fig. 7.1** Etiology of acute liver failure in the United States in 2436 patients. Data from the United States Acute Liver Failure Study Group, sponsored by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases (personal communication Dr. William M. Lee, UT Southwestern Medical Center)



liver injury occurring within 26 weeks after the initial onset of symptoms and in the *absence* of a diagnosis of chronic liver disease, namely cirrhosis [1]. Our usage of this definition recognizes that there is considerable variability in the definition of ALF as it relates to duration of symptoms, and alternate definitions have a role in describing phenotypic differences in distinct subgroups of ALF [2].

ALF is a rare disorder with an estimated incidence in the developed world of <10 cases per million persons with approximately 2000 cases occurring in the United States annually [3, 4]. Principle etiologies associated with the development of ALF include drug toxicity (principally acetaminophen), acute viral hepatitis (A, B, or E), autoimmune hepatitis, Budd-Chiari syndrome, pregnancy related disease, and Wilson disease. Acetaminophen toxicity remains the leading cause of ALF in the United States accounting for approximately 46% of cases in the NIH sponsored United States Acute Liver Failure Study Group (US-ALFSG) registry (Fig. 7.1).

Prognosis in ALF is largely determined by etiology. Etiologies with favorable prognosis include acetaminophen, ischemia, hepatitis A, and pregnancy related disease. Several models have been studied to aid in determining prognosis though all have inherent flaws and the perfect prognostic model does not exist [5]. Perhaps the best known models include the King's College Criteria (KCC) (Box 7.1) and the Model for End Stage Liver Disease (MELD) [6]. The performance of these two models in predicting in hospital mortality in patients with ALF was compared in a recent meta-analysis. The pooled diagnostic odds ratio (DOR) for the KCC was 5.3 (95% confidence interval [CI], 3.7–7.6; 57% heterogeneity) and the DOR for MELD was 7 (95% CI, 5.7–9.7; 48% heterogeneity) thus reflecting similar accuracy between the models with the summary under the receiver operating characteristic curve (ROC) 0.76 for KCC and

0.78 for MELD [7]. In subgroup analysis the KCC performed better than MELD in patients with acetaminophen induced ALF, the KCC DOR was 10.4 (95% CI, 4.9–22.1) compared to 6.6 (95% CI, 2.1–20.2) for MELD; the MELD score performed better in patients with non-acetaminophen induced ALF DOR 8.2 (95% CI, 5.98–11.88) compared to a DOR of 4.16 (95% CI, 2.34–7.40) for KCC [7]. An additional model for predicting transplant free survival in patients with acute liver failure was developed by the US-ALFSG using retrospective data from 1974 patients presenting with ALF. In this logistic regression model, degree of encephalopathy, etiology of ALF, usage of vasopressors, and the laboratory values of serum bilirubin and INR are used. This model predicted transplant-free survival with a C statistic value of 0.84, 66.3% accuracy (95% confidence interval, 63.1%–69.4%), 37.1% sensitivity (95% confidence interval, 32.5%–41.8%), and 95.3% specificity (95% confidence interval, 92.9%–97.1%) [8].

#### Box 7.1 Kings College Criteria for Predicting Poor Outcomes in Patients with Acute Liver Failure

##### Acetaminophen-induced ALF

- Arterial pH < 7.30 after fluid resuscitation

OR all of the following features:

- Prothrombin time >100 s (international normalized ratio >6.5)
- Serum creatinine >259  $\mu\text{mol/L}$  (3.4 mg/dL)
- Grade 3 or 4 hepatic encephalopathy

**Non Acetaminophen-induced ALF**

- Prothrombin time >100 s (international normalized ratio >6.5)

OR any three of the following features:

- Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF
- Time from jaundice to hepatic encephalopathy >7 days
- Prothrombin time >50 s (international normalized ratio >3.5)
- Serum bilirubin >297.6  $\mu\text{mol/L}$  (17.4 mg/dL)

Overall outcomes for patients presenting with acute liver have improved over time, largely due to improvements in intensive care support for these highly complex patients. In a prospective observational cohort study from the US-ALFSG comparing outcomes in two 8-year time periods (1998–2005 and 2006–2013), the 21 day survival rates increased overall from 67.1% to 75.3%; with a transplant free survival increase from 45.1% to 56.1%; post-transplantation survival also increased from 88.3% to 96.3% ( $P < 0.01$  for each) [4].

### 7.3 Chronic Liver Disease

Strictly defined cirrhosis is the “histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury” [9]. Chronic pathologic processes which result in cirrhosis include chronic viral infections, excess alcohol use, non-alcoholic fatty liver disease, autoimmune diseases, genetic diseases of copper and iron metabolism, alpha-1 antitrypsin deficiency, and biliary obstruction amongst others. Regardless of the type of liver insult, ongoing inflammation results in chronic liver disease via two distinct, yet closely related pathological processes. First chronic inflammation leads to activation of hepatic stellate cells which are the key fibrogenic effector cells within the liver. Activation of stellate cells results in deposition of fibrous connective tissue throughout the liver [10]. The progressive deposition of fibrous connective tissue leads to severe disruption of both the vascular and microscopic lobular architecture of the liver leading to portal hypertension. Second, with progressive fibrosis and ongoing hepatocyte injury, extinction of hepatocytes occurs resulting in a decrease in the functional metabolic capacity of the liver.

As an aside, it is important to recognize that liver cell death does not necessarily equate with chronic liver disease.

For example, ALF which results from toxin exposure such as acetaminophen may result in catastrophic death of hepatocytes and resultant liver failure, however patients may fully recover from episodes of ALF; recovery is typically complete and does not result in chronic liver disease. For the purpose of this manuscript, advanced liver disease refers to chronic liver disease and cirrhosis, and specifically excludes acute liver failure. While the term “end-stage” liver disease is frequently used synonymously with cirrhosis among healthcare providers, the authors discourage this practice as it carries a negative prognostic implication in situations where not necessarily appropriate e.g. early well compensated disease.

From a strictly histological perspective, cirrhosis is a yes or no diagnosis. However, from a more practical standpoint, cirrhosis must be understood as a spectrum of disease and is in fact a heterogeneous disorder; clinically cirrhosis is not an “all or none” phenomenon. Indeed patients with early cirrhosis may have few if any overt clinical or biochemical manifestations of liver disease and well preserved liver function, while those with advanced stage cirrhosis often present with multisystem organ failure. Liver fibrosis is progressive in vast majority of cases, however with the advent of improved therapies for many diseases such as curative therapy for chronic hepatitis C infection, we now appreciate that fibrosis may be arrested and in some cases may be reversible [11].

## 7.4 Etiology and Risk Factors for Development of Cirrhosis

### 7.4.1 Viral Disease

Hepatitis B is a DNA virus responsible for development of both acute and chronic liver disease, worldwide it affects between 350 and 400 million people and is responsible for liver related deaths in one million people annually [12]. Hepatitis C virus is an RNA virus infecting 3% of the world population with high prevalence in the Middle East, Asia, and Northern Africa [13]. There are an estimated three million infected in the United States alone, with half of those in the US having undiagnosed disease [14]. Improved antiviral therapies have resulted in treatments which may dramatically alter the course of these diseases. Hepatitis B may be controlled with low incidence of development of viral resistance. Hepatitis C is now curable in a majority of infected patients with vastly simplified regimens. However, the staggering cost of antiviral therapies renders them unobtainable to a majority of infected individuals across the globe at the present time. Further complicating the issue is the fact that millions remain undiagnosed thereby preventing initiation of appropriate therapy. Thus in spite of dramatic advances in treatment, viral hepatitis will remain a major contributor to the development of cirrhosis for the foreseeable future.

### 7.4.2 Alcohol Related Disease

Alcohol misuse is a major risk factor in the development of chronic liver disease worldwide [15] and is the main risk factor for the development of cirrhosis in Europe [16]. In general, there is a dose-response relationship between the amount and duration of alcohol consumption and development of cirrhosis. However it is noted that only 15–35% of heavy drinkers develop cirrhosis [17, 18] thus indicating additional influences are involved in the development of alcoholic liver disease. In addition to genetic influences, previous studies have identified additional risk factors, which when present, increase the chance of developing cirrhosis due to alcohol. These factors include female sex, obesity, smoking, and chronic hepatitis C infection [19, 20]. A recent study by Askgaard et al. evaluated patterns of alcohol consumption as a risk factor for development of cirrhosis, the finding of this study was that daily drinking in men conferred a hazard ratio of 3.65 (95% CI: 2.39–5.55) when compared to drinking only 2–4 days per week [21].

### 7.4.3 Non-alcoholic Fatty Liver Disease

It is generally accepted that non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the world. NAFLD encompasses hepatic steatosis without evidence of liver inflammation and non-alcoholic steatohepatitis (NASH). NASH is a more pathogenic form of NAFLD and leads to the development of fibrosis and cirrhosis [22]. Reported prevalence of NAFLD varies wildly depending on the population studied and the methods used to assess liver pathology (e.g. biopsy vs. non-invasive imaging). A 2011 systematic review by Vernon et al., reports the prevalence of NAFLD in the US at 30% with median worldwide prevalence of 20% [23]. The increasing incidence of NAFLD and NASH mirrors worldwide trends in obesity and the metabolic syndrome [24]. Currently NASH is the third leading cause for liver transplantation in the US and if the current trajectory continues it is expected that it will overtake alcohol and hepatitis C as the leading indication [25].

In addition to the major risk factors for development of cirrhosis listed above, many other disease states result in cirrhosis of the liver.

### 7.4.4 Metabolic Disease

Hereditary hemochromatosis is a disease of iron overload caused by mutations in the HFE gene and is the most common genetic disorder affecting Caucasians with a prevalence of 1 in 220–250 persons with a penetrance of approximately 70% [26, 27]. Patients affected with hemochromatosis suffer

from abnormal iron metabolism with resultant organ damage affecting the liver, heart, pituitary, and pancreas. Cirrhosis and hepatocellular carcinoma are advanced complications in affected individuals. Wilson disease is an autosomal recessive disorder of copper metabolism affecting 1 in 30,000 persons worldwide [28]. Both conditions may result in the development of cirrhosis in absence of proper treatment. In contrast to hereditary hemochromatosis, Wilson's disease may present as acute or chronic liver failure.

### 7.4.5 Autoimmune Disease

A number of autoimmune conditions lead to advanced liver disease. Primary sclerosing cholangitis (PSC) is a disease of the intrahepatic and extrahepatic bile ducts which results in progressive biliary stricturing and may be complicated by development of cirrhosis and cholangiocarcinoma. While believed to be immune mediated, the exact mechanism for disease development has not been fully elucidated [29]. PSC has no known treatment.

Primary biliary cholangitis (PBC) is also a progressive cholestatic disease of the bile ducts (primarily intrahepatic). PBC carries a highly specific autoimmune profile with 90–95% of patients having positive serologies for anti-mitochondrial antibodies, with <1% of healthy controls being positive [30]. PBC does respond to treatment with ursodeoxycholic acid which delays histologic progression of biliary disease and improves transplant free survival [31, 32].

Autoimmune hepatitis, as the name implies, results from a T-cell mediated attack directed against liver antigens with resultant inflammation and fibrosis and frequently responds to immune modulating therapies. The point prevalence of autoimmune hepatitis in Sweden is 10.7/100,000 with 76% of affected persons being female [33]. Men are more likely to suffer relapse however women are more likely to die or require liver transplantation [34]. The clinical course of autoimmune hepatitis varies dramatically and may present as acute liver failure or as essentially asymptomatic disease with indolent course [35].

## 7.5 Epidemiology of Advanced Liver Disease

Advanced liver disease presents a significant global health burden. Worldwide cirrhosis is the twelfth leading cause of death representing just over one million deaths in 2012 [36]. However when one adds deaths attributed to viral hepatitis (B and C) and liver cancer (which occurs largely secondary to cirrhosis and/or viral hepatitis), advanced liver disease becomes the fifth leading cause of death worldwide (Fig. 7.1) responsible for nearly two million deaths annually [36].

Scaglione et al. examined the prevalence of cirrhosis in the United States using the National Health and Nutrition Examination Survey data (NHANES) from 1999 to 2010. The prevalence of cirrhosis in the US is estimated to be 0.27% which corresponds to just over 630,000 adults [37]. A startling finding in this study was that nearly 70% of patients as identified as potentially having cirrhosis could not recall being diagnosed with liver disease [37], thus indicating that this disease with high prevalence remains grossly under recognized. Patients with advanced liver disease frequently require hospitalization, in the 10 years between 2001 and 2011 the total number of cirrhosis hospitalizations nearly doubled from 371,000 to 659,000 while the hospital costs associated with these admissions climbed to \$12.5 billion US [38].

According to the United States Centers for Disease Control (CDC) mortality rates for deaths attributed to cirrhosis rank cirrhosis as the twelfth leading cause of death overall [39]. When analyzed in the context of distinct age groups, liver disease ranks as the seventh leading cause of death in adults aged 25–44, and the fifth leading cause of death in adults aged 45–64 [39]. However the CDC data applies a rather narrow definition for identification of liver disease in its estimates and only utilizes death certificate data in which alcoholic liver disease, chronic hepatitis, and fibrosis and cirrhosis of the liver are listed as the cause of death [39]. Recognizing the flaws in the CDC data, Asrani and colleagues provided a more comprehensive assessment of the true liver related mortality in the US in a 2013 study. In this study, Mayo Clinic researchers utilized expanded criteria to identify deaths directly attributable to advanced liver disease. In addition to the definition used by the CDC, the Mayo group added the following: other liver diagnoses; hepatic failure, unspecified; fatty change of the liver; hepatorenal syndrome; liver disease, unspecified; chronic hepatitis B and C, acute hepatitis B; and hepatobiliary cancer [40]. By applying expanded criteria, the Mayo team estimated the 2008 death rate due to advanced liver disease was 66,007, more than double the CDC estimate of 29,921 [40]. An additional strength of the Asrani study was their comparison of clinical data from Olmstead County, Minnesota using the Rochester Epidemiology Project [41] which served to verify their approach to identifying liver related death.

Given the significant morbidity associated with cirrhosis, it is no surprise that advanced liver disease is responsible for a substantial amount of ICU admissions. It has previously been estimated that there are in excess of 26,000 ICU admissions related to cirrhosis annually with an in-hospital mortality of approximately 50% [42]. The average cost of an ICU admission is roughly \$116,000 and an estimated \$3 billion in annual charges are associated with the ICU care of patients with advanced liver disease [42]. Moreover, while ICU

admissions with many chronic conditions have decreased over time, ICU admissions related to cirrhosis have remained flat (data not published).

## 7.6 Clinical Implications of Advanced Liver Disease: Acute-on-Chronic vs. Decompensated Chronic Liver Disease

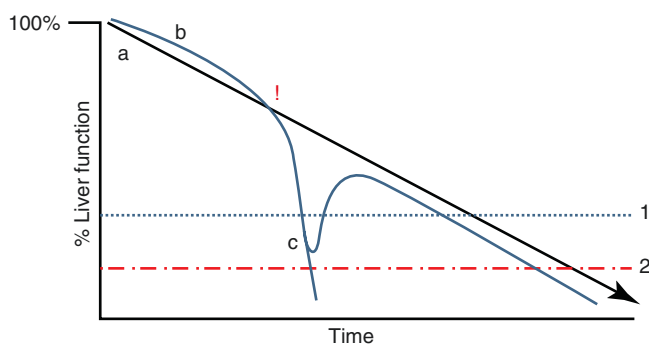
The natural history of advanced liver disease provides that the disease may be broadly grouped into two categories, compensated and decompensated states. In compensated cirrhosis, manifestations of disease are minimal. The transition to decompensated disease occurs when symptoms of cirrhosis manifest in overt symptoms due to progressive architectural disruption and decreasing functional capacity of the liver. The principle events which signify a transition to decompensated disease are the development of esophageal varices, hepatic encephalopathy, or ascites. The transition from compensated disease to a decompensated occurs at a rate of 5–7% per year [43] and has important prognostic implications. Median survival in patients with compensated disease is 12 years and falls to 2 years after decompensation ensues [43]. Accumulation of decompensating events also worsens prognosis, for example a patient who has upper GI bleeding alone has an estimated 5 year mortality rate of 20%, this climbs to 88% after the development of a second decompensating event *e.g.* development of ascites after a variceal hemorrhage [44]. Liver transplantation remains the only curative option for advanced decompensated cirrhosis. Unfortunately in many parts of the world transplantation is not available, and in countries where transplant is available, demand for organs far outpaces supply. It is for these reasons that advanced cirrhosis is a terminal disease for a vast majority of patients suffering from this affliction. The Model for End Stage Liver Disease score (MELD) and its variant the MELD-sodium (MELD-Na) score have been extensively validated as tools to predict short term (90 day) mortality in patients with advanced liver disease [45, 46]. The MELD and MELD-Na scores are now used in many countries to prioritize patients on liver transplant waiting lists thereby giving highest priority to patients with the highest risk for short term mortality.

In addition to the primary manifestations of cirrhosis noted above, decompensated liver disease affects virtually all organ systems. Examples include: disorders of renal function such as abnormalities in fluid handling and overt renal failure (*e.g.* hepatorenal syndrome); gastrointestinal issues such as malnutrition, and motility disturbances; cardiac dysfunction with hyperdynamic circulation and systemic hypotension as well as structural and functional cardiac abnormalities (*e.g.* cirrhotic cardiomyopathy); endocrine



abnormalities resulting in abnormal sodium handling, gynecomastia, osteoporosis, and glucose dysregulation; and pulmonary disorders including portopulmonary hypertension and hepatopulmonary syndrome. All patients with cirrhosis are at risk for development of hepatocellular carcinoma though rates are higher in patients with viral hepatitis who develop hepatocellular carcinoma at rates of 3–8% per year [47]. When identified early, hepatocellular carcinoma is a treatable disease and may be cured with resection or liver transplantation. Because of the complex interactions between the liver and all other organ systems patients with cirrhosis who become critically ill provide distinct challenges for the critical care team.

The last decade has seen a growing interest in the concept of acute-on-chronic liver failure (ACLF) as a unique clinical entity which occurs in patients with chronic liver disease. ACLF is recognized as an acute deterioration of liver function occurring in patients with compensated or stably decompensated liver disease [48, 49]. This phenomenon is frequently associated with a precipitating event (*e.g.* infection or acute variceal hemorrhage) and results in multi-system organ failure, the need for intensive care support, and carries a high short term mortality [50]. In contrast to the natural progression of advanced cirrhosis, which in absence of transplantation is eventually fatal, ACLF when identified and acted upon early may carry an element of reversibility (Fig. 7.2). It is for these reasons advancing our understanding of the concept of ACLF is particularly important for the intensivist caring for patients with cirrhosis in the ICU as it may serve to guide decisions with regard to application of medical therapies and help identify cases in which further aggressive care is futile.



**Fig. 7.2** A schematic representation of acute-on-chronic liver failure. Line (a) represents a patient following the natural history of chronic liver disease. Line (b) represents a patient with compensated disease suffering an acute event (*e.g.* infection or major bleeding event) at the time point marked with (!) and developing acute-on-chronic liver failure. Lines 1 and 2 are arbitrarily drawn at levels of liver function at which decompensation (line 1) and organ failure/death (line 2) ensue. Point (c) demonstrates a significant proportion of patients with ACLF will die from their illness, however many recover

Previously ACLF was largely a theoretical framework which lacked a foundation in clinical trials. However recent work published by the European Association for the Study of Liver Disease-Chronic Liver Failure Consortium (EASL-CLIF) now gives a more evidence based and pragmatic description of ACLF and provides a framework to aid in prognosis of these gravely ill patients [51]. ACLF is defined as acute deterioration of previously compensated cirrhosis with associated organ failures (as defined by the CLIF-sequential organ failure assessment [CLIF-SOFA] score and high short term mortality (>15%) [52]. In this large multi-center European study of 1349 patients hospitalized for complications of cirrhosis, 22.6% had ACLF at time of enrollment and ACLF developed in 10.8% of the 1040 patients without ACLF at time of enrollment within 28 days [52].

Severity of ACLF is graded on the basis of accumulating organ failures; for example patients with ACLF grade 1 include three subgroups of patients: a) patients with single kidney failure, b) patients with single failure of the liver, coagulation system, or respiratory failure and a serum creatinine between 1.5 and 1.9 mg/dL, or c) patients with single cerebral failure with a serum creatinine between 1.5 and 1.9 mg/dL; ACLF grade 2 includes patients with two organ failures; and ACLF grade 3 patients with three or more organ failures [52]. Among patients with ACLF present at time of enrollment the 28 day mortality ranged from 22.1% in ACLF grade 1 to 76.7% in ACLF grade 3 [52]. In a follow up study from the EASL-CLIF consortium a prognostic scoring system was developed and validated which has proven effective in predicting short term mortality in patients with ACLF termed the CLIF Consortium Organ Failure score (CLIF-C ACLFs) [53]. The CLIF-C ACLFs accurately predicated short-term (28-day) and mid-term (90 day) mortality [51]. In addition this tool demonstrated that in patients with ACLF 3 and  $\geq 4$  organ failures and with a CLIF-C ACLFs of  $>64$  there was a 100% mortality rate at 180 days [51]. Usage of this scoring system may prove useful in determining which patients may benefit from consideration of emergency liver transplant and in whom further resuscitative efforts are futile. An online calculator for the CLIF-C ACLFs can be found at <http://www.clifconsortium.com/>.

Though work by the EASL-CLIF consortium, the Asian Pacific Association for the Study of the Liver, and the American Association for the Study of the Liver has continued to advance our understanding of ACLF, differentiating ACLF from true end-stage cirrhosis remains difficult as there is no single sign or test which identifies this entity and therefore practical application of this important concept by the general intensivist remains a formidable challenge.

## 7.7 Discussion

Advanced liver disease is responsible for a significant worldwide health burden. Advances in treatment of viral hepatitis may decrease the overall disease burden of advanced liver disease in the future, however at the present time these therapies are not widely available due to extreme cost. The incidence of non-alcoholic fatty liver disease is also on the rise, thus the worldwide incidence of cirrhosis is likely to continue to increase for the foreseeable future. Patients with advanced liver disease experience extensive medical complications and have a high rate of hospitalization combined with frequent admissions to the ICU. This patient population provides distinct challenges to the intensivist. Treatment options for patients with advanced liver disease are mainly supportive with the only definitive treatment option being liver transplant. Those in need of life saving liver transplant far outnumber organ availability.

Differentiating which patients are truly “end-stage” and thus unlikely to benefit from aggressive life support from those who are suffering ACLF remains difficult. All patients who present to the intensive care unit in the setting of advanced liver disease deserve consultation with transplant specialists to determine if transplant is a potential option. In absence of a viable transplant option and in patients in whom ongoing aggressive life support has failed to improve the overall condition or in patients who have progressive organ failures, the prognosis is dismal. In order to obtain the best outcomes for this difficult population, teams consisting of specialists in critical care, hepatology, and liver transplantation are required.

## References

1. AASLD Position Paper: The Management of Acute Liver Failure: Update 2011. [www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf](http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf).
2. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. *Aliment Pharmacol Ther*. 2012;35(11):1245–56.
3. Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525–34.
4. Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, Durkalski V, Larson AM, Liou I, Fix O, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. *Ann Intern Med*. 2016;164(11):724–32.
5. Wlodzimirow KA, Eslami S, Chamuleau RA, Nieuwoudt M, Abu-Hanna A. Prediction of poor outcome in patients with acute liver failure-systematic review of prediction models. *PLoS One*. 2012;7(12):e50952.
6. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864–71.
7. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College Criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: a meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(4):516–25. e515; quiz e543–e545.
8. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a Model to Predict Transplant-free Survival of Patients With Acute Liver Failure. *Clin Gastroenterol Hepatol*. 2016;14:1199–1206.e1192.
9. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. 2008;371(9615):838–51.
10. Pinzani M. Pathophysiology of liver fibrosis. *Dig Dis*. 2015;33(4):492–7.
11. Povero D, Busletta C, Novo E, di Bonzo LV, Cannito S, Paternostro C, Parola M. Liver fibrosis: a dynamic and potentially reversible process. *Histol Histopathol*. 2010;25(8):1075–91.
12. Dienstag JL. Hepatitis B virus infection. *N Engl J Med*. 2008;359(14):1486–500.
13. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *BMJ*. 2014;348:g3308.
14. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med*. 2013;368(20):1859–61.
15. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373(9682):2223–33.
16. Zatonski WA, Sulkowska U, Manczuk M, Rehm J, Boffetta P, Lowenfels AB, La Vecchia C. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. *Eur Addict Res*. 2010;16(4):193–201.
17. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol*. 2012;57(2):399–420.
18. McCullough AJ, O'Shea RS, Dasarthy S. Diagnosis and management of alcoholic liver disease. *J Dig Dis*. 2011;12(4):257–62.
19. Dam MK, Flensburg-Madsen T, Eliassen M, Becker U, Tolstrup JS. Smoking and risk of liver cirrhosis: a population-based cohort study. *Scand J Gastroenterol*. 2013;48(5):585–91.
20. Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2012;10(8):837–58.
21. Askgaard G, Gronbaek M, Kjaer MS, Tjonneland A, Tolstrup JS. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. *J Hepatol*. 2015;62(5):1061–7.
22. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology*. 2010;52(5):1836–46.
23. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34(3):274–85.
24. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005–23.
25. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141(4):1249–53.
26. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, McLaren CE, Bahlo M, Nisselle AE, Vulpe CD, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med*. 2008;358(3):221–30.

27. Asberg A, Tretli S, Hveem K, Bjerve KS. Benefit of population-based screening for phenotypic hemochromatosis in young men. *Scand J Gastroenterol*. 2002;37(10):1212–9.
28. Mak CM, Lam CW. Diagnosis of Wilson's disease: a comprehensive review. *Crit Rev Clin Lab Sci*. 2008;45(3):263–90.
29. Maggs JR, Chapman RW. An update on primary sclerosing cholangitis. *Curr Opin Gastroenterol*. 2008;24(3):377–83.
30. Gershwin ME, Mackay IR, Sturgess A, Coppel RL. Identification and specificity of a cDNA encoding the 70 kd mitochondrial antigen recognized in primary biliary cirrhosis. *J Immunol*. 1987;138(10):3525–31.
31. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology*. 2009;50(1):291–308.
32. Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. *J Hepatol*. 2003;39(1):12–6.
33. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, Wallerstedt S, Sandberg-Gertzen H, Hultcrantz R, Sangfelt P, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. *Scand J Gastroenterol*. 2008;43(10):1232–40.
34. Al-Chalabi T, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. *J Hepatol*. 2008;48(1):140–7.
35. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010;51(6):2193–213.
36. World Health Organization Global Health Estimates for Cause Specific Mortality 2012. [http://www.who.int/healthinfo/global\\_burden\\_disease/estimates/en/index1.html](http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html).
37. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, Volk ML. The epidemiology of cirrhosis in the United States: a population-based Study. *J Clin Gastroenterol*. 2015;49:690.
38. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology*. 2016;64(6):2165–72.
39. Heron M. Deaths: leading causes for 2012. *Nat Vit Stat Rep*. 2015;64(10):1–94.
40. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology*. 2013;145(2):375–82. e371–372.
41. Melton LJ 3rd. History of the rochester epidemiology project. *Mayo Clin Proc*. 1996;71(3):266–74.
42. Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, Kamath PS. Intensive care of the patient with cirrhosis. *Hepatology*. 2011;54(5):1864–72.
43. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44(1):217–31.
44. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, Tine F, Giannuoli G, Traina M, Vizzini G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment Pharmacol Ther*. 2014;39(10):1180–93.
45. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464–70.
46. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359(10):1018–26.
47. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–2.
48. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on chronic liver failure. *J Hepatol*. 2012;57(6):1336–48.
49. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care*. 2011;17(2):165–9.
50. Olson JC, Kamath PS. Acute-on-chronic liver failure: what are the implications? *Curr Gastroenterol Rep*. 2012;14(1):63–6.
51. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrif L, Hopf C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology*. 2015;62(1):243–52.
52. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7):1426–37. 1437.
53. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, Levesque E, Durand F, Angeli P, Caraceni P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol*. 2014;61(5):1038–47.

# Brain and the Liver: Cerebral Edema, Hepatic Encephalopathy and Beyond

## 8

Gagan Kumar, Amit Taneja, and Prem A. Kandiah

### Abstract

Occurrence of brain dysfunction is common in both chronic liver disease as well as acute liver failure. While brain dysfunction most commonly manifests as hepatic encephalopathy in chronic liver disease; devastating complications of cerebral edema and brain herniation syndromes may occur with acute liver failure. Ammonia seems to play a central role in the pathogenesis of brain dysfunction in both chronic liver disease and acute liver failure. In this chapter we outline the pathophysiology and clinical management of brain dysfunction in the critically ill patients with liver disease.

### Keywords

Hepatic encephalopathy • Acute liver failure • Fulminant hepatic failure • Chronic liver failure • Acute-on-chronic liver failure • Hepatic coma • Intracranial hypertension

### Learning Objectives

- Review the classifications, mechanisms and neuroimaging findings involved in hepatic encephalopathy
- Differentiate the risk factors and implications of hepatic encephalopathy in acute Liver failure and Chronic Liver Failure
- Recognize and distinguish the approach to evaluating and managing hepatic encephalopathy and its confounders in critically ill patients with acute and chronic liver failure
- Outline the organ system approach to ICU considerations in hepatic encephalopathy applicable to acute and chronic liver failure

G. Kumar, M.D.  
Department of Critical Care, Northeast Georgia Health System,  
743 Spring Street NE, Gainesville, GA 30501, USA  
e-mail: [gagankumar@gmail.com](mailto:gagankumar@gmail.com)

A. Taneja, M.D.  
Division of Pulmonary & Critical Care Medicine, Department of  
Medicine, Medical College of Wisconsin,  
8701 Watertown Plank Rd, Milwaukee, WI 53226, USA  
e-mail: [ataneja@mcw.edu](mailto:ataneja@mcw.edu)

P.A. Kandiah, M.D. (✉)  
Division of Neuro Critical Care & co appt. in 5E Surgical/  
Transplant Critical Care, Department of Neurosurgery, Emory  
University Hospital, 1364 Clifton Road NE, 2nd floor, 2D  
ICU-D264, Atlanta, GA 30322, USA  
e-mail: [prem.kandiah@emoryhealthcare.org](mailto:prem.kandiah@emoryhealthcare.org)

## 8.1 Introduction

Hepatic encephalopathy (HE) represents brain dysfunction directly caused by liver insufficiency and or portosystemic shunting (PSS) that manifests as a wide spectrum of neurological and psychiatric deficits ranging from subclinical deficits to coma.

## 8.2 Classification of HE

To capture the complexity and breadth of HE, the recent 2014 combined EASL-AASLD guidelines have integrated four characteristic factors into the classification of HE (see Table 8.1): (1) underlying disease (2) severity of manifestation

**Table 8.1** Classification and grading of hepatic encephalopathy<sup>a</sup>

Classification of HE	Sub classification of HE	Defining feature and description	
1. Underlying disease <sup>a</sup>	Type A	Acute Liver Failure	
	Type B	Portal-systemic Bypass without intrinsic hepato-cellular damage	
	Type C	Cirrhosis and portal hypertension with portal-systemic shunts	
2. Severity of Manifestation <sup>b</sup>	Grade 0	No HE	No HE
		Psychometric or neuropsychological alterations without clinical evidence of mental change	<b>Minimal HE or COVERT</b>
	Grade I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	<b>COVERT</b>
	Grade II	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	<b>OVERT</b>
	Grade III	Somnolence to semi stupor Responsive to stimuli Confused Gross disorientation Bizarre behavior	
	Grade IV	Coma	
	3. Time course of presentation	Episodic	Single or episodes occurring >6 months
Recurrent		Episodes occur <6 months	
Persistent		Behavioral alterations that are always present and interspersed with relapses of overt HE.	
4. Precipitating factors	None		
	Precipitated	Precipitating factors can be identified in nearly all bouts of episodic HE type C and should be actively sought and treated when found	

<sup>a</sup>AASLD-EASL Hepatic encephalopathy Guideline [2]<sup>b</sup>Adapted from West Haven Criteria [1]

(3) time course and (4) precipitating factors. Severity of manifestation was adapted from West Heaven (WH) criteria and merged with three newer definitions: minimal HE, covert HE and overt HE. For this critical care review, we will limit our focus on overt HE (Type A and C). While the WH Criteria [1] remains the staging tool for severity of HE, there remains significant differences in the implications of the grade of HE across the disease categories.

### 8.3 HE, Cerebral Edema and Mortality in ALF and Overt Type C HE

Cerebral edema (CE) at the cellular level (cytotoxic edema) or interstitial level (vasogenic edema) is a pathophysiologic hallmark of HE in both acute and chronic liver failure. In chronic liver failure, the occurrence of CE is not apparent on a macroscopic level. Hence the edema is not visible on conventional brain imaging, causing the clinician no concerns for elevated intracranial pressure (ICP). In acute liver failure, intracranial hypertension (IH) is a looming concern to the clinician. The term intracranial hypertension (IH) specific to ALF, implies

both a cause and effect. The cause refers to diffuse CE visible on brain imaging and the effect refers to elevated ICP and impending transtentorial herniation if left untreated.

Acute liver failure (ALF) is a devastating disease with mortality up to 40–50% due to progressive multiorgan failure [3]. Worsening HE in ALF heralds a grim a prognosis. Grade IV HE precedes the development of cerebral edema and IH culminating in transtentorial herniation. Historically the progression from HE to transtentorial herniation accounted for up to 75–80% of deaths in ALF [4, 5]. With improved ICU care focusing on neuroprotective interventions, the mortality attributable to IH is in the range of 10–20% [6].

Despite the absence of IH, the diagnosis of HE in chronic liver failure is associated with a 50% mortality at 1 year. The correlation between Type C HE and increased mortality in cirrhosis has been difficult to decipher due the heterogeneity of the occurrence and impact of accruing multi-organ failure. Acute-on-chronic liver failure (ACLF) remains a term in search of a more precise definition that accurately captures a dominant subset of decompensated cirrhotics with disproportionately high short-term mortality rates attributable to multiorgan failure. In the recent European Canonic study,

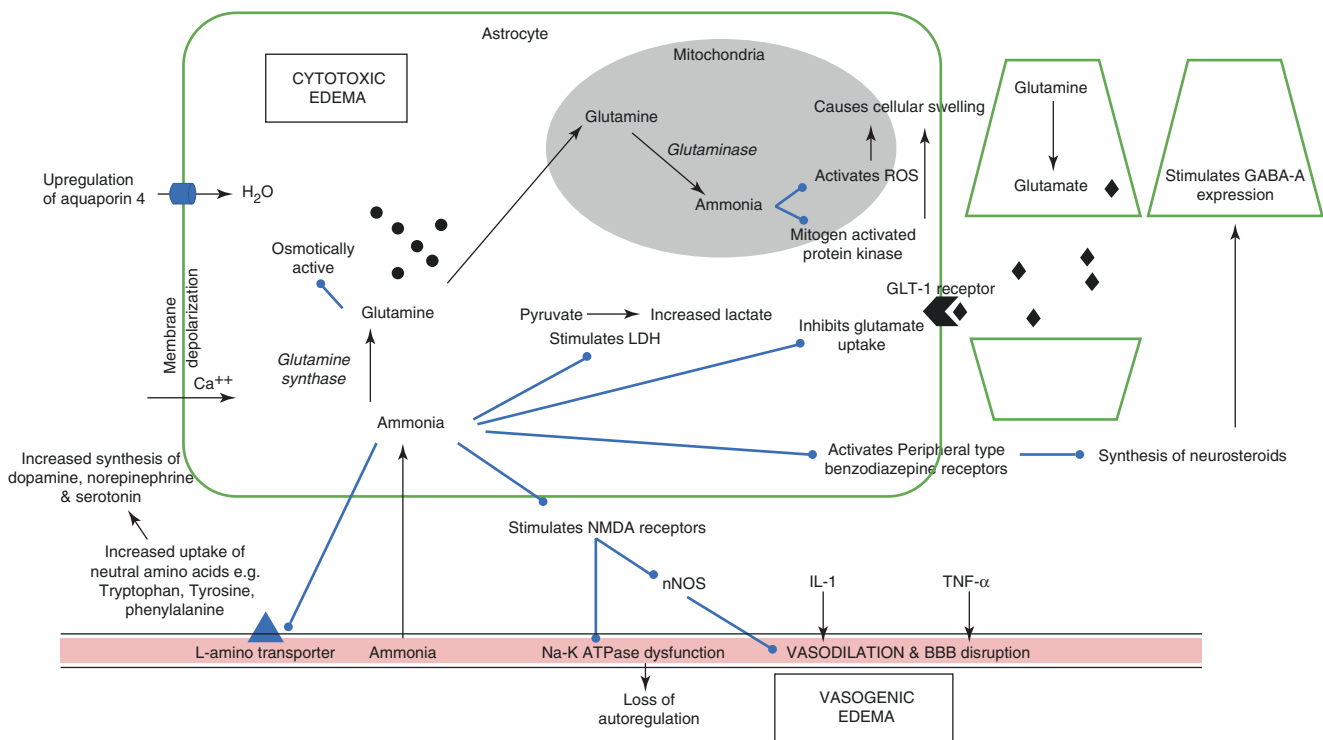


ACLF was distinctly defined by the sequence and severity of organ dysfunction, allowing for a better understanding of the implications of HE in this critically ill subgroup [7, 8]. HE in both decompensated cirrhosis and ACLF was independently associated with increased mortality. However, mortality from HE associated with ACLF was significantly worse than the HE associated decompensated cirrhosis [9] and therefore warrants closer monitoring and early transfer to the ICU.

Unlike ALF, IH does not occur in decompensated cirrhosis but is infrequently reported in ACLF [10, 11]. The rare occurrence IH in ACLF is predicated upon the acuity of the liver injury rather than the chronicity of the liver disease [12]. A more recent retrospective study noted that cerebral edema leading to tonsillar herniation and death was observed in 4% (3/48) of patients with ACLF [13].

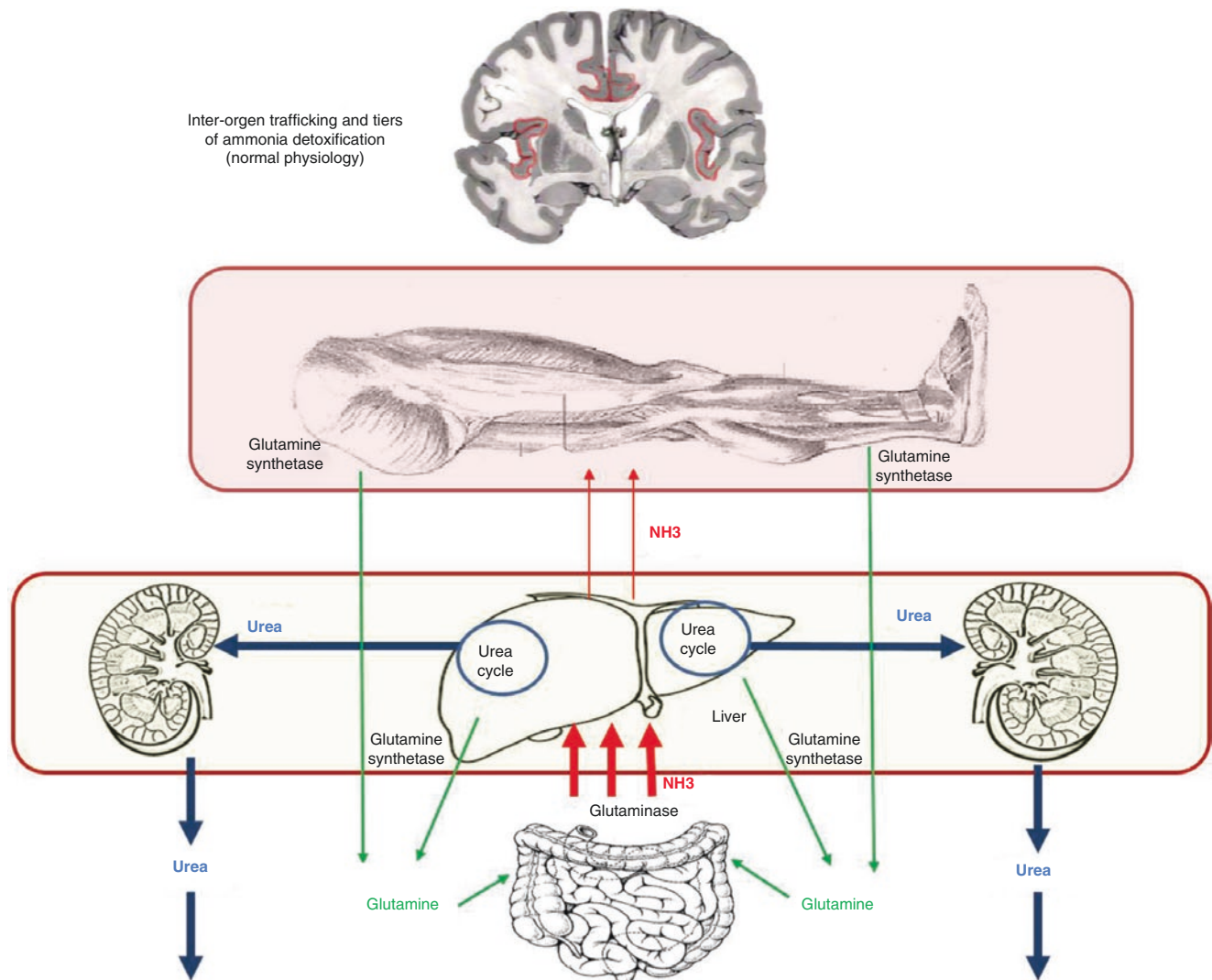
## 8.4 Pathophysiology

There remains no singular attributable etiology for HE. HE is a result of a complex interplay between brain ammonia, inflammation, altered neurotransmission pathways and cerebral hemodynamic dysautoregulation. Hyperammonemia continues to play a significant role in pathogenesis of HE [14, 15]. Ammonia is also thought to result in both cytotoxic and vasogenic brain edema, cerebral energy failure, excessive intracellular accumulation of the osmolyte glutamine and alterations in aquaporin-4 integral membrane proteins [16–19]. Ammonia also causes membrane depolarization, calcium influx, glutamate release, activation of proteases and production of free radicals which causes nitration of neuronal proteins and mitochondrial damage [19–21]. Figure 8.1



**Fig. 8.1** Hypothesized neurotoxic mechanisms of hyperammonemia: Multiple pathways of ammonia related neurotoxicity have been discovered and postulated. Most significantly they affect astrocytes where ammonia is converted into glutamine. Glutamine has multiple deleterious effect in the CNS. Glutamine results in elevated synaptic glutamate levels and inhibits GLT-1 receptor thus preventing its reuptake. Glutamate stimulates postsynaptic receptors of neurons causing anxiety, agitation and convulsions. Glutamine is taken up by astrocyte mitochondria where it is reconverted into ammonia. This in turn stimulates ROS production in mitochondria, subsequently causing inflammation and cellular swelling through mitogen activated protein kinase. Glutamine is itself osmotically active and worsens swelling. Aquaporin 4 is upregulated by ammonia and IL-1 and is associated with cellular swelling. Ammonia also stimulates L-amino transporter in BBB, thus increasing uptake of neutral amino acids like tryptophan, tyrosine and phenylalanine. These compounds are building blocks for dopamine, norepinephrine and serotonin in CNS. It also results in stimulation of

NMDA (N-methyl d-aspartate) receptors which mediates Na-K-ATPase dysfunction resulting in loss of autoregulation. Ammonia also causes membrane depolarization, calcium influx, glutamate release, activation of proteases and production of free radicals which causes nitration of neuronal proteins and mitochondrial damage. Ammonia also stimulates lactate dehydrogenase activity with subsequent formation of lactic acid and alanine. Hyperammonemia can result in increased neurosteroids production leading to elevated GABAergic tone in CNS. The loss of integrity of blood brain barrier results in formation of vasogenic edema. Hyperemia caused by failure of ATPase pump leads to loss of autoregulation of cerebral blood flow. Increased activity of neuronal nitric oxide synthase (nNOS) by ammonia toxicity results in nitric oxide production. In addition, cyclo-oxygenase gene is upregulated resulting in increased production of prostaglandins and eicosanoids which may contribute to hyperemia and increased cerebral blood flow. There is also evidence that there is microglial activation in ALF resulting in increased production of TNF alpha, IL-1 and IL-6



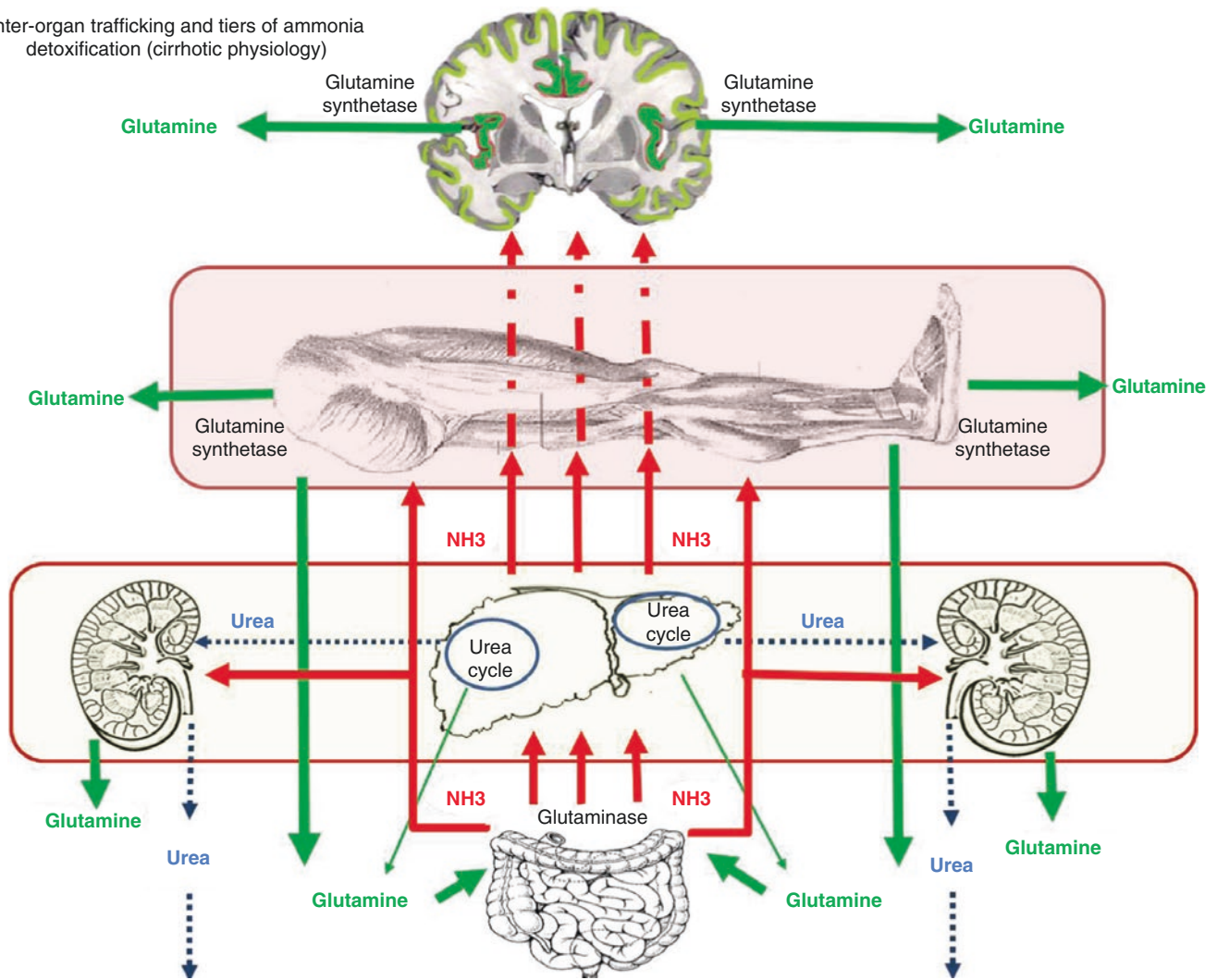
**Fig. 8.2** Simplified conceptual model of interorgan trafficking and tiers of detoxification of ammonia in normal physiology: Dietary and circulating glutamine are converted by bowel endothelial cells to ammonia in the in the entero-hepatic circulation. Abnormal liver function and portosystemic shunting results in a large amount of ammonia entering the systemic circulation and breaching the first tier of detoxification. In end-stage cirrhosis, the significant loss of muscle mass further compromises the second tier of ammonia detoxification and exposes the brain to higher concentration of plasma ammonia.

Astrocytes particularly in select regions of the cortical grey matter have the capacity to detoxify ammonia to glutamine by using glutamine synthetase enzyme. However, when overwhelmed with this process, glutamine accumulates intracellularly in the astrocytes and becomes osmotically active and causes a cytotoxic edema. Note that ammonia detoxification generates large amount of circulating glutamine which cannot be eliminated except indirectly via the kidneys. Renal impairment which is common in cirrhosis will intensify the severity and frequency of hepatic encephalopathy

provides a graphic representation of the various neurotoxic mechanisms in hyperammonemia. The homeostasis of ammonia is complex process dependent on multiple organ systems. Ammonia generated in the gut is detoxified to glutamine and urea by the liver and urea in turn is excreted by the kidneys. Defective sequential detoxification of ammonia by liver and kidney due to multi-organ failure in ALF and ACLF appreciably accounts for worsening HE. Muscle and brain (astrocytes) represent auxiliary ammonia detoxification systems that convert toxic ammonia to glutamine. Resultant glutamine accumulation in astrocyte is osmotically

active and thus causes intracellular swelling (cytotoxic edema) [16, 22, 23] Hence, in the cachectic and catabolic end-stage cirrhotic, skeletal muscle provides minimal refuge to the brain from ammonia. A measured plasma ammonia level in a patient only discloses a small fraction of the proverbial ice berg, with the net bulk of the ammonia concealed in the form of glutamine. Excess glutamine can only be cleared indirectly via intact liver and renal function [24–26], without which glutamine becomes a precursor to generating more ammonia. Figures 8.2 and 8.3 provides a simplified graphic representation of this process.

Inter-organ trafficking and tiers of ammonia detoxification (cirrhotic physiology)



**Fig. 8.3** Simplified conceptual model of interorgan trafficking and tiers of detoxification of ammonia in cirrhotic physiology: Dietary and circulating glutamine are converted by bowel endothelial cells to ammonia in the entero-hepatic circulation. Abnormal liver function and portosystemic shunting results in a large amount of ammonia entering the systemic circulation and breaching the first tier of detoxification. In end-stage cirrhosis, the significant loss of muscle mass further compromises the second tier of ammonia detoxification and exposes the brain to higher concentration of plasma ammonia.

Astrocytes particularly in select regions of the cortical grey matter have the capacity to detoxify ammonia to glutamine by using glutamine synthetase enzyme. However, when overwhelmed with this process, glutamine accumulates intracellularly in the astrocytes and becomes osmotically active and causes a cytotoxic edema. Note that ammonia detoxification generates large amount of circulating glutamine which cannot be eliminated except indirectly via the kidneys. Renal impairment which is common in cirrhosis will intensify the severity and frequency of hepatic encephalopathy.

Malignant cerebral edema resulting in intracranial hypertension and brain herniation appears to rely on secondary mechanisms specific to ALF. While cytotoxic edema is an explicit feature in HE, its immediate contribution to malignant edema or intracranial hypertension is dubious. In cirrhotics with HE, cytotoxic edema is present on a cellular level but often unappreciable on CT imaging. Vasogenic edema is thought to lag temporally behind cytotoxic edema and is both direct and indirectly attributable to ammonia [27–29]. Luxury perfusion due to increased cerebral blood flow and impaired autoregulation appears to be a process specific to ALF that accounts for the development of malignant cerebral edema

and intracranial hypertension. Mechanisms driving this process include the loss of integrity of blood brain barrier [18], failure of ATPase pump with resultant hyperemia due to loss of cerebrovascular autoregulation, increased NO production due to increased activity of neuronal nitric oxide synthase [30], up regulation of cyclooxygenase with increased production of prostaglandins and eicosanoids resulting in hyperemia and increased cerebral blood flow [30]. Hyponatremia frequently occurs in ALF and likely contributes to increased interstitial water and the cerebral edema. Targeting higher plasma sodium goal is associated with a lower incidence of intracranial hypertension.

In chronic liver failure, the brain has time to adapt to the deleterious effects of chronic ammonia exposure. Cerebral astrocytes have the capacity to convert ammonia into glutamine. In chronic liver failure, intracellular glutamine accumulation is offset by the export of organic osmoles (myo-inositol and taurine) from astrocytes to maintain osmotic balance and mitigate the development of cytotoxic edema.

Glutamine in turn prevents reuptake of glutamate which accumulates in post synaptic space. In chronic liver failure, there is compensatory decrease in glutamate receptors in post synaptic membrane which may account for the psychomotor slowing and drowsiness seen in HE. Other mechanisms of HE includes the elevated GABAergic tone produced by stimulation of TGR5 receptors and increased neurosteroid production by activation of peripheral type benzodiazepine receptors.

The failing liver triggers a systemic inflammatory response with activation of immune system and release of cytokines including IL-6, IF- $\alpha$ , TNF- $\alpha$ . The mechanism of increased cytokines involves activation of toll like receptors which activate Kupffer cells that activate signaling cascades and transcription of proinflammatory cytokines. These cytokines increase cerebral blood flow and increase permeability for ammonia. While this process contributes to HE in chronic liver failure, it transpires on a mammoth scale in ALF.

## 8.5 Clinical Features of Hepatic Encephalopathy in Chronic Liver Disease

In the undifferentiated liver failure patients with abnormal synthetic liver function, the absolute first critical step is to distinguish if the HE is type A (ALF) or type C (Chronic). This step helps stratify risk attributable to the HE and designates appropriate neuromonitoring and neuroprotective interventions. While this may seem intuitive, confusing these disease entities is not uncommon in clinical practice and results in unnecessary delays that affect patient outcome. In autoimmune hepatitis, differentiating the two can at times be difficult due to derangements in synthetic function common to both in early stages. A careful history, and longitudinal monitoring of neurological status and synthetic function will be needed to make this determination. In the indeterminate phase, it is prudent to adopt an ALF management strategy until the clinician can safely determine the acuity and chronicity of the disease.

If the initial presentation of HE in chronic liver failure is atypical or severe (grade 3 or 4 HE), excluding an alternate etiology due to infection, metabolic anomaly, toxidrome, neurovascular event or seizures through an accurate history, physical exam, laboratory work up and brain imaging is paramount. If the mental status decline of HE (grade 1 to grade 4) is witnessed with typical features and a precipitant identified, extensive work up for an alternate etiology is less warranted.

## 8.6 Neurological Assessment in Early HE

Evaluating orientation and serial subtraction test to assess attention are one of the more objective determinations of earlier stages of HE specifically WH grade I to II. Other neuropsychiatric findings are more subjective and can be difficult to quantify and trend. The more contemporary Confusion Assessment Method (CAM ICU) and Agitation Sedation Scale (RASS) used in ICUs may provide some additional benefits to discriminating the neuropsychiatric changes and the level of arousal respectively, however, neither have been adequately validated in HE [31].

An additional efficient and objective method to monitor progression or recovery from HE focusses on grading asterix by quantifying the number for flaps over 30 s (see Table 8.2) [32]. Coarse tremor or jactitation [33], while common to HE should not be mistaken for asterix. Negative myoclonic jerks differentiable from asterix in HE can be observed frequently in opioid toxicity and uncompensated respiratory acidosis and less commonly in severe uremia and other neurological disorders.

In more severe grades of HE, using the Glasgow Coma Scale is useful, appropriate and has been validated in HE and may provide more immediate information about the neurological trajectory. One limitation WH criteria as well as other developed HE scales [34, 35] have is the ceiling effect for patients in who are in coma. Glasgow Coma Score allows a more refined discrimination of advanced grades of HE (see Table 8.3).

**Table 8.2** Grading asterix to monitor progression of hepatic encephalopathy [32]

Grade of asterix	Description	Number of flaps/30 s
Grade 0	No flapping motions	0
Grade I	Rare flapping motion	1–2
Grade II	Occasional, irregular flaps	3–4
Grade III	Frequent flaps	5–30



**Table 8.3** Comparable Glasgow Coma Scale to Modified West Haven Criteria adapted from Bernal et al. [36]

West Haven Criteria Grade	GCS
I	14–15
II	12–15
III	7–12
IV	<7

## 8.7 Physical Exam in HE

A complete neurological examination in severe HE is likely to uncover false localizing signs including transient pupillary dysfunction, dysconjugate gaze, gaze deviation, ocular bobbing, decorticate and decerebrate posturing, hyperreflexia, up going plantar as well as other less common findings. These findings are usually transient and resolve or change within hours. Cases of reversible focal deficits mimicking stroke attributable to severe HE has been reported but fortunately these are not common.

## 8.8 Brain Imaging in Overt Type C HE

In patient with low grade HE (WH grade I or II) developing sudden focal deficits i.e. face, arm and leg weakness that is clinically localizable, a CT if negative for hemorrhage should be followed up by an immediate CT-Angiogram before considering thrombolytics. MRI would also be helpful in this situation if it can be performed quickly. Initiating thrombolytics with a negative CT alone would not suffice due to the coagulopathy and higher bleeding risk in cirrhotics and the potential that the source of the deficit was predominantly a metabolic abnormality and not a vascular phenomenon.

In a single center study of 158 cirrhotic patients scanned for altered mental status, Joshi et al. revealed that 30% of head CTs were normal, 30% demonstrated increased atrophy, 17% with small vessel disease and 16% with intracranial hemorrhage [13]. The prevalence of intracranial hemorrhage (ICH) in ACLF was higher than decompensated cirrhosis: noted to be 23% versus 9% [13]. Given this finding, the decision to image a patient HE requires clinical discretion. If a patient with recurrent HE, presents with his/her usual presentation for HE that was witnessed by family or hospital staff, then imaging would less likely be of use. If an unresponsive patient was found on the ground, demonstrates evidence of trauma from a fall, witnessed fall or atypical presentation of HE, imaging with CT should be performed. Findings by Joshi et al. also implies that a lower threshold for performing CT

should be considered in patients with ACLF possibly due to the more coagulopathic state evidenced by lower platelet counts, higher INRs and lower fibrinogen levels.

While the risk of IH leading to herniation is low in cirrhosis, the infrequent occurrence IH in ACLF (4%) is predicated upon the acuity of the liver injury rather than the chronicity of the liver disease [12, 13]. Therefore, infrequently, an obtunded ACLF patient with abrupt deterioration in synthetic liver function, who is relatively young, with significant hyperammonemia, hemodynamic instability, multi-organ failure, hyponatremia, very recent TIPSS procedure or volume overload should be considered for imaging to evaluate for cerebral edema and herniation.

MRI may be useful in evaluating atypical features or refractory HE for alternate causes, both common and rare. More recently, an underrecognized complication of prolonged course of metronidazole used for management of HE in cirrhotics with impaired renal function has been identified with explicit MRI finding [37–39]. MRI may also detect cerebral edema more precisely than CT however, the infrequent ACLF patients suspected of having cerebral edema is likely too critically ill to tolerate an MRI.

## 8.9 Precipitating Factors for Overt Type C HE

Reversible precipitating factors have been reported in up to 80% of patients with cirrhosis. Prompt recognition of precipitating factors and common confounders help identify a reversible cause and refines the approach to investigation and treatment (see Table 8.4). In addition to well-known precipitating factors for HE, Table 8.4 also delineates frequently overlapping confounders seen in patients with cirrhosis that should be considered and assessed when deemed clinically relevant by history and physical exam.

In the recent European Canonic study, infection remains a major precipitant of episodic HE, recurrent HE as well as HE in ACLF. Unlike prior studies, GI bleeding appeared to confer a lower risk for developing HE [2, 40]. Earlier endoscopic interventions and improved management strategies for GI bleeds may have contributed to this paradigm shift. More notably, the European Canonic Study was able to identify a distinctive difference in clinical characteristics of patients with HE due to ACLF compared with HE associated with decompensated cirrhosis (see Table 8.5). Active alcohol use surfaced as a precipitant of HE that was unique to patients with ACLF. Table 8.5 differentiates clinical features and precipitants of HE in ACLF versus decompensated cirrhosis.



**Table 8.4** Precipitating factors, HE-confounders and underlying mechanisms in hepatic encephalopathy

Mechanism	Precipitating Factor and HE-confounders	Work up to consider
Excess nitrogen burden	Gastrointestinal bleed <sup>a</sup> Blood transfusions Constipation <sup>a</sup> Azotemia Excess dietary protein Protein catabolism in starvation and insulin resistance due to Diabetes Mellitus <sup>a</sup> Portosystemic shunt <sup>a</sup> (iatrogenic and spontaneous)	Complete blood count BUN and Creatinine Micronutrients—B12, B6, Thiamine, Carnitine level Plasma ammonia levels Blood Glucose and HbA1c Abdominal venous imaging
Infection and inflammation	Infection <sup>a</sup> SBP <sup>a</sup> Septic shock Viral or Autoimmune Encephalitis Cryptococcal Meningitis HIV/AIDS Pancreatitis	Blood, Urine, CSF, Sputum culture, C. difficile toxin Ascitic fluid cell count and culture ScvO2 and Lactate Serum and CSF Cryptococcus antigen HIV serology Lipase and amylase
Compromised toxin clearance	Dehydration due excessive fluid restriction, diuretic use <sup>a</sup> or paracentesis <sup>a</sup> , diarrhea Acute Kidney Injury, Hepatorenal Syndrome Hypotension due to bleeding <sup>a</sup> , or systemic vasodilatation Abdominal Compartment syndrome due to severe ascites	Renal function Electrolytes (serum Sodium) ScvO2 and Lactate Monitor Bladder Pressures
Compromised neurotransmission and metabolism	Endoepines and neurosteroids Benzodiazepine use Coinciding Alcohol withdrawal Opioid Use Psychoactive drugs Hypoglycemia Hypoxemia and Hypercarbia Thyroid dysfunction	Urine Toxicology Blood alcohol level Blood Glucose ABG TSH
Acute hepatocellular damage	Alcoholic hepatitis <sup>a</sup> Drugs Other acute hepatitis Development of hepatocellular carcinoma Undiagnosed Wilsons Disease	Liver function panel Acetaminophen Level Acute Hepatitis work up Alpha fetoprotein level Serum and 24-h urinary Copper, Ceruloplasmin,
Other confounders: metabolic abnormalities, neurological injury	Intracranial Hemorrhage (Subdural Hemorrhage is most common cause) Dementia Wernicke's encephalopathy Metronidazole induced encephalopathy Central Pontine Myelinolysis Brain Stem Strokes Severe Hyperammonemia Seizure disorder	Head CT MRI brain with and without gadolinium EEG

ABG arterial blood gas, CSF cerebrospinal fluid, HIV human immunodeficiency virus, ScvO2 central venous oxygen saturation, TSH thyroid-stimulating hormone

<sup>a</sup>Precipitating factors of HE specific to chronic liver failure. Data from American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014;61(3):642–59; and Cordoba J, Ventura-Cots M, Simon-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol 2014;60(2):275–81.

**Table 8.5** List of clinical features and precipitating factors for HE in decompensated cirrhosis versus ACLF—canonic study<sup>a</sup>

	HE in decompensated cirrhosis	HE in ACLF
Clinical features	<ul style="list-style-type: none"> <li>• Older Cirrhotics</li> <li>• Inactive Drinkers</li> <li>• Less impairment of Liver function</li> <li>• Minimal inflammatory reaction</li> <li>• Low prevalence of organ failure</li> <li>• Lower mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Young Cirrhotics</li> <li>• More frequently Alcoholics</li> <li>• More Impairment in Liver function</li> <li>• Increased inflammatory response</li> <li>• High prevalence of organ failure</li> <li>• Higher mortality</li> </ul>
Precipitating factors	<ul style="list-style-type: none"> <li>• Long term diuretic use</li> </ul>	<ul style="list-style-type: none"> <li>• Active alcohol use</li> <li>• Bacterial infections</li> <li>• Hyponatremia</li> </ul>

<sup>a</sup>Data from Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, Angeli P, Domenicali M, Gines P, Bernardi M et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). Journal of hepatology 2014, 60(2):275–281.

**Case 1**

55 year old male with Hepatitis C related Cirrhosis is having recurrent HE occurring frequently and causing recurrent admissions. In addition to his liver disease, he has stage III Chronic Kidney Disease for which is being evaluated for a combined Liver and Kidney Transplant. He is being treated with a HE regime of daily doses of Lactulose, Rifaximin, Zinc and Metronidazole for the last 12 weeks for the refractory HE. He has become increasingly altered in the past week and presents to the Emergency department with seizures that subsided with Ativan 2 mg and was subsequently intubated.

**Exam:**

Heart rate: 90 bpm Respiratory Rate: 12 bpm BP: 112/70 Temperature: 36.8 °C

Neuro: Pupils 3 mm reactive to light. Brisk reflexes throughout with upgoing plantar reflexes. Remains minimally responsive with GCS 7. Moving all four extremities with equal strength.

CVS: Normal heart sounds. Sinus rhythm. No murmurs

Pulmonary: Clear to auscultation bilaterally

GI: Ascitic abdomen and nontender to palpation.

Extremities: Normal pulses. Trace edema.

**Laboratory and Diagnostics:**

His plasma ammonia level is 89 mmol/L. He is afebrile. Ascetic fluid cell count is normal. Urine analysis with 12 wbc and the urine has been sent for culture. His chemistry

panel and liver function panel remains unchanged from his last outpatient visit. EEG revealed periodic lateralizing discharged from both parietal lobes suggesting cortical irritability for which Levetiracetam IV has been initiated.

**Question:**

1. What diagnostic test would you order?
2. How would you treat his encephalopathy?

**Answer:**

1. MRI brain
2. Discontinue Metronidazole. Continue Lactulose and Rifaximin.

This is a case of Metronidazole Induced Encephalopathy (MIE). The patient is at risk due to decreased clearance with both liver and kidney dysfunction. Metronidazole is not infrequently used off label to treat refractory HE. When used indiscriminately, accumulation of Metronidazole causes neurotoxicity affecting both peripheral nerve and central white matter. This patient had bilateral symmetrical parietal white matter demyelination and edema seen on MRI which is consistent with MIE. With supportive care, management of seizure and discontinuing metronidazole, most patient will improve with time. Limit Metronidazole use in cirrhosis to 7 days or less when possible.

## 8.10 Goals of Therapy for HE in Chronic Liver Failure

1. Identifying if HE is presenting with decompensated cirrhosis versus ACLF.
  - (a) ACLF patient will require earlier transfer to the ICU due to imminent short-term mortality
2. Treatment of precipitating factors in parallel with intensive care supportive strategies for multiorgan failure
3. Initiation of first tier therapeutic strategies specific to HE
  - (a) Reduction of intestinal ammonia production and absorption
  - (b) Nutritional and micronutrient supplementation
4. Initiation of second tier therapeutic strategies specific to HE
  - (c) Plasma ammonia lowering devices and non-pharmacological interventions
  - (d) Eliminating large spontaneous portosystemic shunts (SPSS)

- (e) Alternative pathway therapies
- (f) Neurotransmitter blockade

Distinction of ACLF has been discussed previously and the importance of this will not be repeated here. Vast majority of patients with HE have a precipitating cause: some of the commoner precipitating causes are upper GI bleeding, infections including spontaneous bacterial peritonitis, hypovolemia and over-diuresis, hypokalemia, metabolic alkalosis, concomitant use or abuse of other sedating drugs, particularly benzodiazepines. Precipitating cause should be actively sought and treated in parallel with best supportive care. Most patients with cirrhosis have protein energy malnutrition and as such there is no role of protein restriction in management of acute or chronic HE. Hypokalemia should be corrected. Hyponatremia should be avoided particularly in ALF and ACLF: however rapid correction of Na avoided due to risk of osmotic demyelination syndrome.

## 8.11 Therapeutic Strategies for Managing Type C HE in the ICU

### 8.11.1 Plasma Ammonia Lowering Strategies (First Tier)

#### 1. Reduction of intestinal ammonia production and absorption

##### (a) Lactulose (beta-galactosidofructose) and Lactitol (beta-galactosidosorbitol)

Despite the absence of mortality benefit, both these nonabsorbable disaccharides are currently first line agents for the treatment of HE. Lactitol is not available in the United States. Since there is absence of specific disaccharidases on the villous membranes of the human small bowel, these disaccharides freely reach the colon. In the colon, they are broken by the colonic bacteria into acids which lowers the pH. This acidification favors conversion of ammonia ( $\text{NH}_3$ ) into ionic ammonium ( $\text{NH}_4^+$ ). Because of its very nature, ammonium ion is less permeable than ammonia and less absorbed into portal circulation. In addition, both lactulose and lactitol inhibit ammoniagenic coliform bacteria and clear ammonia by decreasing transit time. Lactulose is superior to placebo and tap water enemas and comparable to neomycin [41, 42]

Lactulose is usually given orally in patients who are awake enough to swallow. Initial dose of 30–60 ml can be repeated hourly till there is a bowel movement and then dose titrated to 2–3 soft bowel movements per day. Caution should be exercised in patients with significant alteration in mental status and high aspiration risk. In addition, it should be recognized that goal of lactulose administration is not profuse diarrhea: resulting hypovolemia may actually make encephalopathy worse. Finally, lactulose can cause significant gaseous small bowel distension in paralytic ileus and make it worse. A distended abdomen in a critically ill cirrhotic patient receiving lactulose should be evaluated for an ileus and not assumed to be increased ascites. Lactulose can also be given as enema in comatose patients and those unable to swallow or lacking enteral access.

##### (b) Polyethylene Glycol (PEG)

A small randomized single center study demonstrated that a 4 L PEG administered orally or via NG over 4 h led to more rapid HE resolution despite less ammonia difference at 24 h compared to standard therapy with Lactulose. PEG's safety profile and balanced electrolytes make it an attractive adjunct to Lactulose in the ICU setting. Volume of 4 L remains a concern for aspiration especially in later grades of HE.

#### 2. Ammonia lowering antibiotics (First Tier)

(a) **Rifaximin:** Rifaximin is an oral nonsystemic antibiotic with <0.4% absorption. Rifaximin has *in vitro* antimicrobial activity against Gram-positive and Gram-negative, aerobic and anaerobic flora. Current AASLD/EASL guidelines only recommend rifaximin as an add-on therapy for prevention of overt HE recurrence. Data is insufficient regarding the use of rifaximin as a first line therapy or stand-alone therapy for treatment of overt HE. Rifaximin may be used in combination with lactulose in patients with overt HE as the combined effect leads to reversal of the condition in 76% of patients vs. 50.4% in those on lactulose alone. In absence of more robust data, rifaximin 550 mg po q12h is a reasonable adjunct for severe or refractory HE, especially since it has a better side effect profile than neomycin and metronidazole. Rifaximin added to lactulose is more efficacious than lactulose alone in prevention of overt HE (43)

(b) **Neomycin:** Oral neomycin is minimally absorbed, yet chronic administration can result in nephrotoxicity and ototoxicity. Evidence for use and efficacy of neomycin in HE is not robust at all, yet it is FDA approved [43, 44]. For acute HE, 1 g q6h for up to 6 days and for chronic HE, 1–2 g daily is prescribed. Given other alternatives and lack of strong evidence, use of neomycin should probably be limited

(c) **Metronidazole:** Not FDA approved for management of HE. One small study revealed it is as effective as Neomycin at a dose of 250 mg twice daily [45]. The concern for resistant *Clostridium difficile* colitis and neurotoxic effects of metronidazole are valid. Liver failure and renal impairment are both predisposing factors to developing metronidazole encephalopathy (MIE), a toxidrome more recently characterized by both reversible and irreversible findings on MRI [37–39].

#### 3. Nutritional and micronutrient supplementation (First Tier)

(a) **Zinc:** There are a number of small studies on Zinc supplementation in cirrhosis resulting in lower plasma ammonia levels and improved hepatic encephalopathy. The biochemical rationale is predicated on Zinc being a co-factor in the urea cycle. Two recent meta-analysis on zinc in HE revealed a significant neuropsychiatric improvement measured using the number correction test [46]. In the meta-analysis by Timbol et al. published in abstract form., zinc supplementation provided for a statistically significant reduction in serum ammonia levels [47]. Zinc levels are tightly associated with liver function. Cirrhotics with low zinc levels have a higher risk of hepatic decompensation and hepatic encephalopathy. In cirrhosis with

hypoalbuminemia, low zinc levels may be reported since 80% of zinc in blood is albumin bound. Zinc levels are not routinely monitored unless a way to measure free plasma zinc level is developed. In the critically ill patient with HE, including zinc supplementation has the potential to improve ammonia metabolism with minimal side effects. However, long term use of zinc supplementation in concomitant renal failure does increase the possibility of zinc toxicity.

- (b) **L-Carnitine:** There are numerous small studies and anecdotal reports about the ammonia lowering effects of oral supplementation with L-Carnitine which requires further study. Carnitine is a co-factor in the metabolism of long chain fatty acids. It facilitates mitochondrial membrane transport by binding acyl-CoA molecules and promotes translocation from cytoplasm to mitochondrial matrix for B-Oxidation. Disruption in Carnitine transport results in cytosolic accumulation of fatty acyl-CoA molecules which is postulated to inhibit the urea cycle [48]. Patient with carnitine deficiency due to malnutrition or short gut, valproate acid, primary deficiency due to mutations in organic cation transporter gene (OCTN2) have been reported to manifest with symptomatic hyperammonemia which improves with carnitine supplementation. There is limited evidence on use L-Carnitine routinely in the management of HE, however, in cirrhotic patients with a significant history of malnutrition and refractory hyperammonemia, checking L-Carnitine levels followed by supplementing L-Carnitine pending the return of these levels is physiologically sound and may provide a benefit with minimal risk until further evidence is available.
- (c) **Branched-chain amino acid (BCAA) supplementation:** Improvement in HE has been noted in patients predominantly treated in the outpatient setting without improvement in mortality. Existing evidence revealed no difference between BCAA, lactulose and neomycin. It did however increase the risk of nausea and vomiting. Its role in the ICU remains unproven. Having an alternative to lactulose in patients on vasopressors or at risk of developing an ileus could be useful in the critical care setting.

#### 4. Plasma Ammonia lowering devices and non-pharmacological interventions (second Tier)

##### (a) Continuous Renal Replacement Therapy

Continuous renal replacement therapy using continuous veno-venous hemofiltration with high filtration volume (90 ml/kg/h) is an effective method of rapidly lowering serum plasma ammonia levels [49, 50]. Ammonia clearance is closely associated with ultrafiltration rate. More than likely, CRRT will be

used in such a patient for acute kidney injury needing renal replacement; and not hyperammonemia per se. However, one can make a case for CRRT for severe hyperammonemia particularly in ALF or ACLF where the risk of intracranial hypertension and herniation is significantly higher. Hemodialysis and CRRT remains the mainstay for the management of hyperammonemia in patients with urea cycle disorders with a proven track record.

##### (b) Molecular Adsorbent Recirculating System (MARS) and Bio-artificial devices

Molecular Adsorbent Recirculating System (MARS) is a blood detoxification system based on albumin dialysis that removes protein bound (bile acids, bilirubin, endogenous benzodiazepines, nitrous oxide) and water soluble toxins (ammonia, creatinine). In the US, MARS is FDA approved for management of ALF due to drug overdose or toxic exposures and for management of HE in decompensated cirrhosis. MARS trials thus far have failed to show a survival benefit; however they have consistently demonstrated improvement in HE and a satisfactory safety profile. Using MARS for refractory HE is thus a potential option. In the case of bioartificial systems, the extracorporeal circuit includes bioreactors loaded with liver cells, thus theoretically having potential to improve synthetic function as well. These extra-corporeal liver assist devices are as of now far from ideal and not widely available; these are subject of research.

##### (c) Therapeutic Hypothermia (Goal Temperature of 34 °C)

There remains limited clinical experience in the use of mild hypothermia in chronic liver failure [51]. Its appeal in liver disease is that it counteracts many of the metabolic effects of ammonia, slows protein catabolism and production of ammonia by bacteria and the kidneys [52]. The predominant concern with using hypothermia in cirrhotic patients is its potential to worsen the existing coagulopathy in patients who are high risk for bleeding and the predisposition to infection. In rare cases of extreme refractory hyperammonemia, hypothermia can be used as a transient neuroprotective strategy while pursuing clearance of plasma ammonia through other avenues.

#### 5. Alternative pathway therapy (second Tier):

##### (a) Ammonia scavengers: Sodium Benzoate, phenylacetate, glycerol phenylbutyrate, Ornithine phenylacetate

##### (b) L-Ornithine L-Aspartate (LOLA)

Ammonia scavengers help to increase ammonia clearance and thus reduce systemic concentrations of ammonia. These compounds provide an alternative

pathway wherein ammonia is excreted in the urine as phenylacetylglutamine. Whereas small randomized studies show encouraging results, larger trials are needed to define the role of these in HE in daily practice. Limitation of these therapies include the need for intact renal function for elimination of phenylacetylglutamine. Efficacy of therapy with dialysis remains unclear. Sodium benzoate is an FDA approved food additive/preservative and is infrequently off-label in refractory hyperammonemia by adding it to enteral feeding in patients with refractory hyperammonemia and intact renal function. However, the efficacy of this therapy in cirrhosis have not been verified in large trials.

**L-ornithine L-aspartate (LOLA):** LOLA is substrate for urea cycle and stimulates enzymatic activity in residual hepatocytes leading to increased urea excretion. LOLA significantly improves HE and ammonia levels when compared to placebo; however it demonstrated no difference compared with lactulose. Oral LOLA is more frequently used for treatment of HE outside the US.

## 6. Neurotransmitter Blockade (second Tier)

**Flumazenil:** In a systematic review involving 13 controlled trials with a total of 805 patients, the use of flumazenil was associated with significant improvement in HE but failed to show long term benefits or improvement in outcome [53]. As a short acting benzodiazepine antagonist, flumazenil is postulated to inhibit endogenous GABAergic substances and previous residual effects of long acting benzodiazepine. Cirrhotics have also been shown to have increased benzodiazepine receptor activation but only a subset of patients will demonstrate response to Flumazenil. Flumazenil should be used in a closely monitored environment as it has a potential of provoking seizures. A trial of 1–2 mg of Flumazenil in 20 mL saline solution by intravenous infusion for 3–5 min may be considered in patients with stage 3–4 encephalopathy who have low serum ammonia level and have not responded to Lactulose.

## 7. Surgical Treatment Options if applicable (second Tier)

- (a) **Embolization of large portosystemic shunts (PSS):** A review by Lyn AM et al. of their carefully selected 20-patient experience with embolization of portosystemic shunt for refractory HE revealed that durable benefit in HE was achieved in majority of patients with reduction in hospitalization for HE [54]. Increased ascites was noted in about 50% of these patients. Multiple case reports and case series have corroborated these findings, however, larger support-

ing studies especially in the ICU setting remains deficient. PSS embolization could be considered in the refractory, recurrent or persistent HE in select patients. At present, this option is probably underutilized given that imaging for large portosystemic shunts are often not routinely performed for evaluation of refractory HE.

- (b) **Liver transplantation:** is the definitive treatment for HE [55]. Tier 1 and 2 interventions should be thoughtfully and diligently employed to patients eligible for transplant as pre-transplant encephalopathy post-transplant metabolic encephalopathy. An awake, oriented and responsive candidate is also a more attractive candidate for transplantation.

## 8.12 Acute Liver Failure

### 8.12.1 Clinical and Laboratory Assessment Specific to Type A HE (ALF)

In type A HE due to ALF, grading scales for HE do not differ from type C HE (see Neurochecks in HE) which include clinical assessment WH grading, asterix grading, GCS. However, the consequences of progressing to grade 4 HE is significantly worse in ALF due to the significantly higher risk of IH resulting in brain herniation. It is imperative that early determination of acuity of the liver failure need to be ascertained which should trigger a rapid transfer of the patient to a regional liver transplant program. ALF patients can rapidly decline clinically with distributive shock and multiorgan failure after which they are too unstable to a transfer.

### 8.12.2 Neuro Checks in ALF

Monitoring pupillary function is important in WH grade 3 and 4 HE. Pupillary light reaction frequently progresses from normal to hyper-responsive in early in WH grade 2-3 HE and hypo-responsive in WH grade 4 [56]. Loss of pupillary function may be a metabolic phenomenon in late stages however it may also signify brain herniation due to uncus compression or stretching of ciliary fibers of cranial nerve III. Hence, despite the false positive findings, close monitoring of pupils is critical in ALF. Reversal of brain herniation using osmotherapy is possible if detected early.

Reports of up to one third of WH grade IV ALF patients may develop subclinical seizures. Presence of subclinical seizures are of uncertain relevance but could contribute to elevated ICP inpatients with IH. Continuous EEG should be considered during the management of Grade IV HE with risk factors for developing IH.



### 8.12.3 Objectives of Serial Laboratory Testing Relevant to HE and IH in ALF

1. Analyze and monitor the onset and severity ALF and examine for evidence spontaneous recovery of liver function. Risk of cerebral edema is analogous to severity of liver dysfunction and hyperammonemia but resolution of cerebral edema may lag behind the recovery of synthetic liver function.
2. Decelerating the development cerebral edema:
  - (a) Monitor plasma sodium levels, osmolality, pH, CO<sub>2</sub>, plasma ammonia levels
  - (b) Correct hyponatremia, severe acidosis, hypercarbia
  - (c) Augment plasma sodium levels and osmolality
3. Monitoring other organ function, detection of infection and hemodynamic laboratory markers pertinent to cerebral perfusion and brain edema.
4. Triggering the decision to transplant based upon clinical picture in conjunction with biochemical markers before losing the hemodynamic window.

### 8.12.4 Risk Factor for Development of IH in ALF

Plasma ammonia level of more than 150–200  $\mu\text{mol/L}$  is associated with the development of IH in ALF. More recently, Kitzberger et al. reported that 25% of ALF patients developed IH despite relatively low plasma ammonia levels ( $\text{NH}_3 < 146 \mu\text{mol/L}$ ) [57]. The disproportionately higher extra-cerebral severity of organ failure (SOFA) score in these patients emphasizes the substantial role of inflammation and shock organ failure in the development cerebral hyperemia and diffuse cerebral edema. Other common associations for ICP eleva-

tion include hyponatremia, volume overload, severe hypercarbia, severe acidosis, pain and ventilator dyssynchrony.

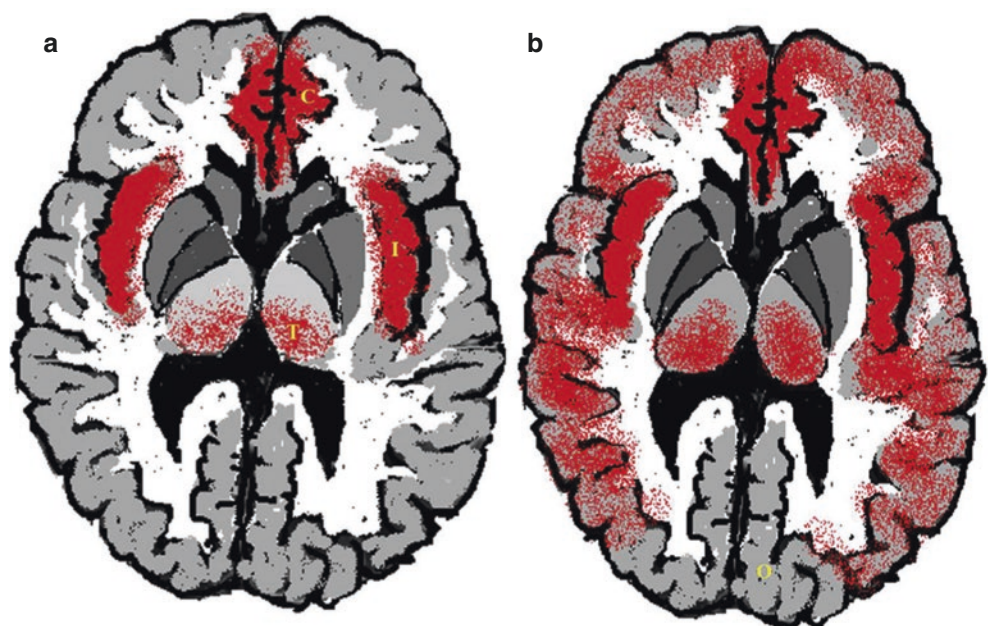
### 8.12.5 Brain Imaging in ALF and IH

Utility of brain CT for assessment of cerebral edema and IH remains in question especially when interpretation of CT is performed without a comparator. Imaging is useful for excluding other intracranial processes or evaluating for complications of placing intracranial devices [58, 59]. If imaging is to be used for CE detection and to assess risk of herniation, performing serial imaging with a baseline scan performed early on before onset of severe HE may be more useful [60].

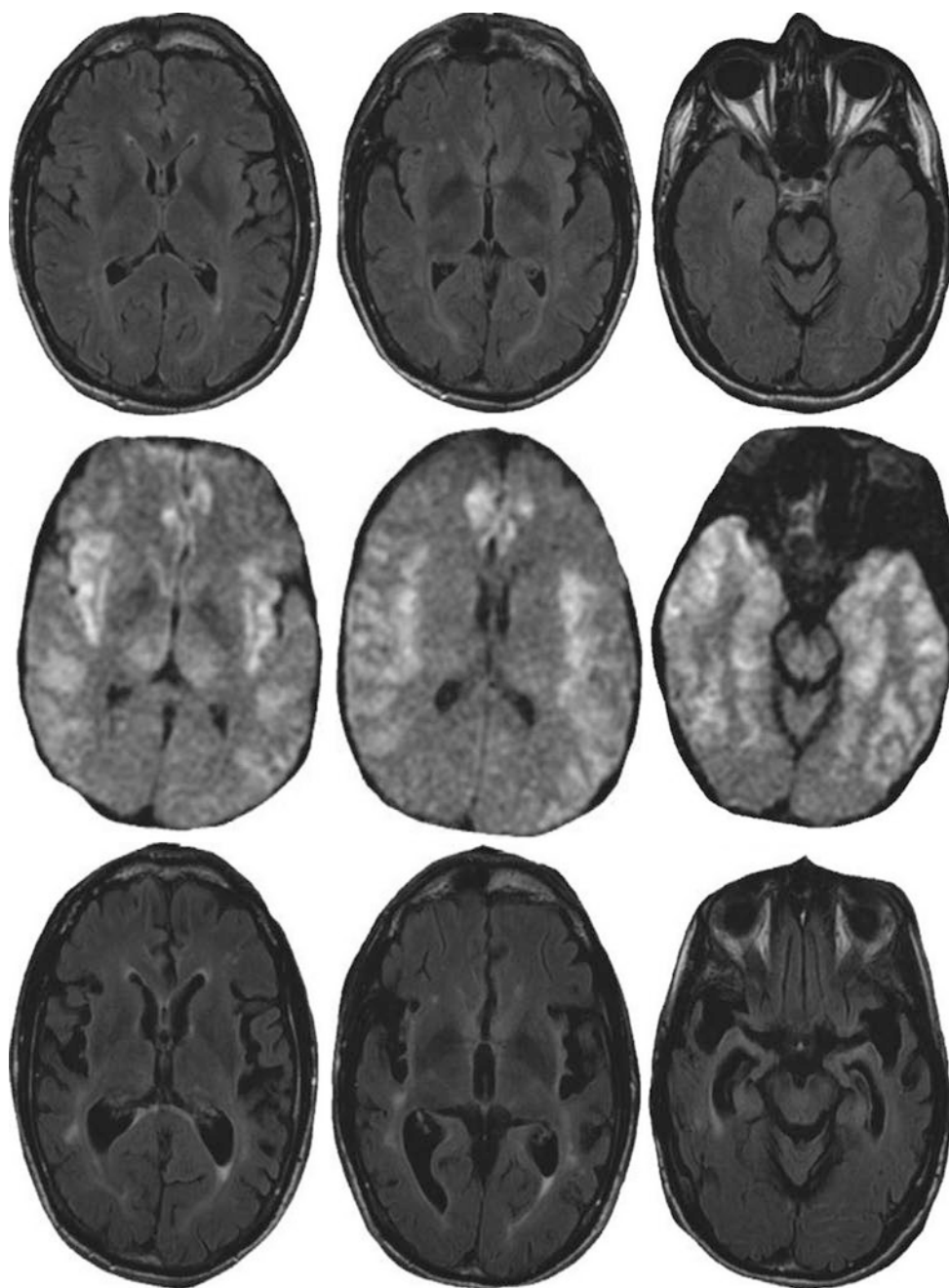
Brain MRI may help exclude CNS infection, brainstem stroke, Wernicke's encephalopathy, metronidazole encephalopathy, and central pontine myelinolysis not visible on CT and should only be pursued if there is a high index of suspicion. If clinically unstable and MRI is necessary, the patient should be monitored by intensive care unit (ICU) clinicians throughout image acquisition.

A recent MRI finding associated with sustained hyperammonemia reinforces the idea that ammonia is neurotoxic and not just an epiphenomenon in HE [61, 62]. Restricted diffusion limited to bilateral insular cortex, cingulate gyrus, and thalamus when mild (limited cortical restricted diffusion [LCRD]) and can involve bilateral temporal, parietal, and frontal lobes and sparing the occipital poles, when severe (diffuse cortical restricted diffusion [DCRD]). This MRI finding is associated with severe hyperammonemia, cognitive decline, matching downstream cortical atrophy, and worse outcome (see Figs. 8.4 and 8.5).

**Fig. 8.4** (a) LCRD—Initial pattern of cytotoxic edema in severe hyperammonemia. Involves insular cortex (*I*), cingulate gyrus (*C*), and thalamus (*T*) with good outcome. (b) DCRD—Diffuse pattern of cytotoxic edema with variable outcome. Involves all cortical grey matter and thalamus with sparing of the occipital poles (*O*)



**Fig. 8.5** MRI features of hyperammonemia in a patient with liver failure. A 49-year-old man with hepatitis C, MELD score 17, with accidental chronic acetaminophen overdose, SOFA score 11, and peak plasma NH<sub>3</sub> level of 606 mmol/L. Plasma ammonia level was <100 mmol/L for 6 days. (Top) Baseline outpatient MRI findings 6 months prior for headache workup. (Middle) Diffusion weighted images during admission for liver failure. DCRD involving bilateral cingulate gyrus, insular cortex, temporal lobes, frontal lobes, and posterior thalamus. (Bottom) Cortical atrophy matching areas of restricted diffusion on 9-month follow-up MRI. Moderate-to-severe static cognitive impairment (From Kandiah PA, Pandya D, Lynch JR, et al. Catastrophic hyperammonemia: a case series. *Neurocritical care* 2008;8(1):61–232; and Kandiah PA, Pandya D, Nanchal R, et al. Metaanalysis of magnetic resonance imaging findings and neurological outcomes in liver failure and severe hyperammonemia. In: 15th International Society for Hepatic Encephalopathy and Nitrogen Metabolism: 2012. Grenaa, Denmark, 2012. pp. 25–6; with permission.)



## 8.13 Pharmacologic Treatment Options

### 8.13.1 Outline of management of HE in ALF

1. Identify and treat cause of ALF to minimize further injury
2. Identify risk factors for mortality and IH (Table 8.6) and evaluate candidacy for liver transplant if high risk
3. Elect neuromonitoring strategy
  - (a) Invasive—intracranial monitoring devices
  - (b) Noninvasive—GCS, neuro checks, pupillary exam, serial brain imaging, transcranial Doppler (TCD), jugular bulb oxymetry, optic nerve sonography
4. Initiate neuroprotective strategies to delay development of CE and IH
  - (a) Head of bed elevation with neck in neutral position
  - (b) Initiate osmotherapy with hypertonic saline or mannitol
    - Crucial to plan an effective osmotherapy strategy taking into account continuous reno-renal replacement therapy (CRRT)
    - Hypertonic saline with sodium goal of 145–150
  - (c) Initiate plasma ammonia lowering strategies
    - Early initiation of CRRT
    - Targeted temperature management (Mild hypothermia 35 °C) [36, 63, 64]

- Avoid hypokalemia and metabolic alkalosis [65]
- Other plasma ammonia lowering interventions
- (d) Consider intensive care supportive strategies for multiorgan failure directed at cerebral edema (see Table 8.7)
- 5. Rescue maneuvers to control elevated intracranial pressure or refractory IH
  - (a) Maintain adequate cerebral perfusion pressure
    - Vasopressors for shock
  - (b) Increased sedation for metabolic suppression
    - Thiopental or Pentobarbital only as a last resort
  - (c) Maximize osmotherapy with hypertonic saline
    - Hypertonic saline with goal sodium of 150–155
    - 20% Mannitol with
  - (d) Consider continuous neuromuscular blockade infusion for high central venous pressures (>20 mmHg) or sustained refractory ICP

**Table 8.6** Risk factors associated with intracranial hypertension in ALF

Risk factors of IH	Possible mechanisms and rational
1. Meets Kings college Criteria	Correlates with severity of liver injury, luxury cerebral perfusion due to inflammation
2. Plasma ammonia level >150 $\mu\text{mol/L}$ [28, 29, 57]	Neurotoxic effects of plasma ammonia <ul style="list-style-type: none"> <li>• Predicts IH with specificity of 84% and a sensitivity of 60%</li> </ul>
3. Plasma ammonia level >200 $\mu\text{mol/L}$ [29]	Neurotoxic effects of plasma ammonia
4. Partial Pressure of ammonia or unionized ammonia (pNH <sub>3</sub> ) [57]	Neurotoxic effects of plasma ammonia
5. Sustained elevation on plasma ammonia levels	Neurotoxic effects of plasma ammonia
6. Acute renal failure requiring CRRT [29]	i) Volume overload impeding venous return. ii) Severe acidosis iii) Decreased clearance of ammonia and glutamine.
7. Young age (<35 years) [29]	Limited intracranial space with limited age related atrophy
8. Vasopressor use [29]	i) Inflammation and multi-organ failure causing vasogenic CE from luxury cerebral. ii) Volume overload due to excessive volume resuscitation
9. Severity of Organ failure (SOFA score) [57]	i) Inflammation and multi-organ failure causing vasogenic CE from luxury cerebral. ii) Volume overload due to fluid resuscitation and oliguric renal failure iii) Decreased ammonia clearance with renal failure <ul style="list-style-type: none"> <li>• Predicts IH with specificity of 62% and a sensitivity of 94%</li> </ul>

**Table 8.7** Intensive care supportive strategies directed at cerebral edema in ALF

Organ system	Intensive care supportive strategies
Neurological	Use short acting sedatives and opiates once intubated. Propofol and low dose fentanyl are sedatives of choice. Avoid intermediate or long acting benzodiazepines.
Respiratory	<b>Intubation</b> for airway protection needs to be considered early in later stages of HE before significant aspiration and lung injury occurs. <b>Low tidal volume</b> lung protective strategy to prevent ARDS. High intrathoracic pressures result in cerebral venous outflow obstruction [66] <b>High Peep</b> → Use cautiously as very high peep can theoretically add to hepatic congestion <b>CO<sub>2</sub> goal:</b> 30–40 mmHg → Hypercarbia causes vasodilatation
Cardiovascular	<b>Noninvasive approach</b> and IH suspected → Target a higher MAP goal ( $\geq 80$ mmHg) <b>Invasive approach</b> → Cerebral perfusion pressures (CPP) should be maintained between 50 and 60 using vasopressors [67] <b>In refractory shock</b> → consider plasma exchange to maintain optimal CPP. Plasma exchange was associated with reduction in SIRS response, reduction in SOFA scores and decline in need for vasopressor support [63, 68] <b>CVP goal &lt; 20</b> → Increased CVP may impede venous return from the brain [69]. Maintain euvolemia. Consider paralysis.
Renal, acid base disorders and electrolytes	<b>Early CRRT</b> → To maintain euvolemia, augment ammonia clearance [49], correction of electrolyte and acidosis correction Formulate strategy to maintain sodium goal (145–150) while on CRRT. Options include preparation of hypertonic prismsate or hypertonic saline infusion in post filter return arm of CRRT. <b>Caution:</b> Initiating CRRT with isotonic prismsate in patient with IH and induced hypernatremia can cause rebound edema from dialysis disequilibrium syndrome and precipitate brain herniation. <b>Hypokalemia and metabolic acidosis</b> increases renal ammonia production. <b>Metabolic alkalosis</b> promotes formation of NH <sub>3</sub> <sup>+</sup> from (NH <sub>4</sub> <sup>+</sup> ) augmenting its passage across the blood brain barrier (15, 16)
GI, liver and nutrition	Abdominal compartment syndrome may indirectly worsen ICP. <b>Lactulose</b> → Avoid lactulose via oral or NG route in ALF as it may cause bowel distention, worsening ileus and complicating transplant surgery. Limited evidence supporting its use in ALF. If used, it is safer to be given rectally
Endocrine	<b>Avoid hypoglycemia</b> → may add to metabolic injury to the brain. Initiate 10% or 20% Dextrose preemptively in ALF
Hematologic and immune system	<b>Disseminated intravascular coagulation</b> → Consider repeating head CT the patient if DIC occurs as spontaneous intracranial hemorrhages may occur.

ARDS acute respiratory distress syndrome, CVP central venous pressure, DIC disseminated intravascular coagulation, MAP mean arterial pressure, PEEP positive end-expiratory pressure, SIRS systemic inflammatory response syndrome

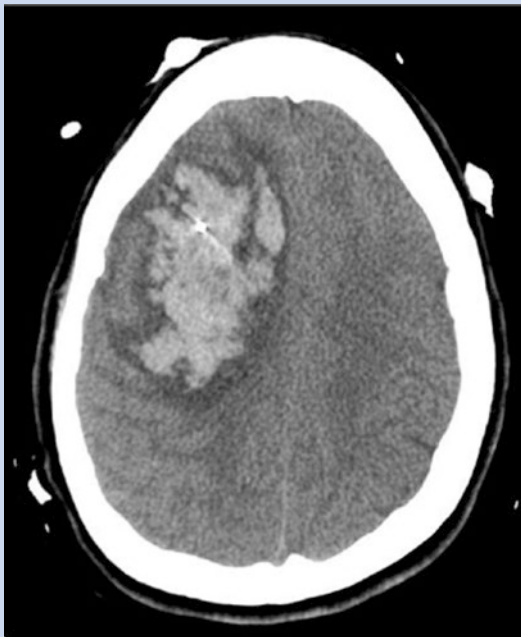


- (e) Targeted temperature management (Moderate hypothermia 33–34 °C)
  - (f) Consider using IV indomethacin 0.5 mg/kg bolus for refractory ICP
  - (g) Correct severe acidosis with sodium bicarbonate infusions
6. Slow de-escalation of neuroprotective therapies post-liver transplant or in transplant free recovery
- IH frequently lag behind liver recovery.
  - Slow normalization of serum sodium levels
  - Monitor for rebound edema or dialysis disequilibrium syndrome
  - Slow rewarming to if induced hypothermia initiated

### Case 2

26 year old woman with cerebral edema after acetaminophen overdose now with grade 4 encephalopathy, renal failure, NH<sub>3</sub> of 300 mmol/L. The decision to place an intraparenchymal ICP monitor (Camino) was made given the high risk status and that patient was not a transplant candidate. She remained hemodynamically stable and on minimal ventilator settings. Intraparenchymal catheter placed after 2 units of FFP, 1 unit of Cryoprecipitate, 1 pack of platelets, and within 1 h of dosing recombinant factor VIIa which produced a resultant INR of 1.4. Platelet count was 104. Post ICP monitor placement, the patients ICP climbs from 15 to 30 mmHg and subsequently 40 mmHg despite sedation and osmotherapy with hypertonic saline.

What is your immediate next step?



Answer: Emergent Head CT

CT head revealed a large right intraparenchymal hemorrhage with midline shift in the region of the ICP pressure probe. Correction of coagulopathy may not be completely protective. Hyperemia of the brain likely contributes to the brisk bleeding when it does occur.

## 8.14 Invasive Neuromonitoring Strategy in ALF

ICP monitoring has been used to identify and treat elevated ICP aggressively especially when brain edema was the predominant cause of death [28, 70]. With improvement in ICU interventions and lower incidence of IH, the utility of invasive intracranial monitoring has been steadily decreasing. Intracranial hemorrhage from bolt placement is reported to range from 2.5% to 10% [71, 72]. While observational studies have not found overall survival advantages in those receiving ICP monitoring [73, 74], the possibility of benefit in a subset of high risk brain edema patients remains unanswered. Recombinant Factor VII<sub>a</sub> is frequently used to help correct the coagulopathy associated with ALF before the procedure [75, 76]. When ICP monitoring is performed, the mean cerebral perfusion pressures (CPP) should be maintained between 50 and 60 using vasopressors [67].

### 8.14.1 Noninvasive Neuromonitoring Strategy in ALF

A non-invasive strategy would be reliant upon empiric use of cerebral edema-preventing interventions as listed below without the reassurance of having a pressure reading. Serial CT imaging [58, 59], Transcranial Doppler, jugular bulb oximetry, pupillometry neurological exam would be complementary to this approach.

Transcranial Doppler ultrasound (TCD) is a non-invasive method to estimate ICP based on waveform characteristics due to resistance in cerebral blood flow in proximal cerebral circulation [77]. Its utility in ICP detection in ALF has not been validated prospectively and has to be interpreted with caution. Trends in TCD indicating cerebral perfusion could be useful however an easy method for continuous monitoring is not yet available [78]. Other non-invasive devices such as optic nerve sonography, technologies using near infrared spectroscopy and pupillometry have not been validated in ALF.

### 8.14.2 Neuroprotective Strategies in ALF

**Hyponatremia** can worsen cerebral edema and thus should be treated but care must be taken to avoid rapid correction.

**Hypertonic saline** used to prophylactically to elevate serum sodium level between 145 and 155 meq/L has been demonstrated to reduce the incidence and severity of IH in HE grade 3 and 4 patient a single center study [79]. 30% hypertonic saline infusion titrated between 5 and 20 mL per h to maintain serum sodium levels at 145–155 mmol/L was used in this study.

**Hyperosmotic agents** have been traditionally used to reduce ICP. This approach may also be used in patients with elevated ICP in ALF patients [80]. Twenty percent Mannitol in bolus doses of 0.5–1 g/Kg bodyweight can be used to reduce ICP. Serum osmolality should be monitored while on mannitol and should be kept <320 mOsm/L due to risk for renal tubular toxicity. However there is no evidence for this number [81]. Care should be taken in patients with ARF, use of mannitol can cause volume overload from osmotic effect of drawing water from interstitial space.

**Hyperventilation** causes hypocapnia that induces alkalosis which in turn produces vasoconstriction and thereby a decrease in CBF and cerebral blood volume hence decreasing ICP. However, there is a serious concern of hypocapnia causing or worsening cerebral ischemia and rebound cerebral edema [82]. Moderate short term hyperventilation reduces global cerebral blood flow without compromising cerebral oxidative metabolism [83].  $\text{PaCO}_2$  should be monitored and should be targeted between 30 and 40 mmHg [84].

**Barbiturate coma** may be considered with pentobarbital in selected cases [85]. Thiopental and pentobarbital have been shown to reduce brain oxygen utilization, however, in setting of ALF, neurological assessment cannot be done due to induced coma and the half-life is prolonged due to hepatic metabolism of this drug. Pentobarbital is associated with hemodynamic instability due to the direct myocardial suppression effect and should be used and monitored with caution. Bowel dysmotility and frequent occurrence small bowel ileus is a well known adverse effect of barbiturates. Therefore, NG lactulose should be avoided in barbiturate use altogether.

**Hypothermia** has been successful in decreasing ICP and has been reported to help to bridge to liver transplant [86–88]. Its use in ALF remains controversial as two studies (Temp 33–34 °C) have demonstrated both absence of benefit and harm [64, 89]. Sustained and significant reduction in plasma ammonia levels [87] and its utility in controlling ICP remains an attractive intervention in the ICU and perhaps should be reserved for refractory IH or refractory hyperammonemia.

**Indomethacin** reduced ICP by cerebral vasoconstriction in a porcine model [90]. In a physiological study of 12

patients with ALF, IV bolus of indomethacin dose of 0.5 mg/kg reduced ICP and increased CPP without compromising cerebral perfusion. Further studies need to be performed prior to considering it for routine use. IV formulation of indomethacin is not easily available in the US.

**Seizures** can worsen cerebral edema and increase ICP. Since one third of patients with ALF have seizures, continuous EEG monitoring should be considered in patients who are both sedated and paralyzed [91]. Phenytoin was shown to reduce breakthrough seizures in one small study while using it prophylactically was of no benefit in another [92]. While phenytoin is indicated in breakthrough seizures in ALF, its side effect profile and liver induction effects should preclude its prophylactic use. It is not unreasonable to consider the use of newer antiepileptic medications with less side effect profiles and not metabolized by the liver to treat breakthrough seizures in HE.

**CRRT** is recommended over hemodialysis due to lower fluctuations in ICP and improved hemodynamic stability [93, 94]. CRRT is particularly effective at lowering plasma ammonia levels [49] and correcting hyponatremia. Appropriate consideration should be given to sodium concentration in dialysate for CRRT and intravenous hypertonic saline dosing when determining goal serum sodium level.

### 8.14.3 Plasma Ammonia Lowering Strategies in ALF

Ammonia plays a significant but fragmented role in the development of cerebral edema and IH. There remains a paucity of studies that show therapeutic benefit to ammonia reduction. While Lactulose and Rifaximin may offer a nominal plasma ammonia reduction effect, they are likely deficient in preventing IH in ALF. Unlike cirrhosis, ALF patients are not preconditioned to deal with hyperammonemia and are likely more susceptible to ammonia related toxicity. In practice, plasma ammonia reduction in ALF is frequently orchestrated habitually and serendipitously by using CRRT [49] for acute renal failure and therapeutic hypothermia [87] IH. Earlier use of CRRT for significant hyperammonemia, despite relatively preserved renal function, may delay the development of cerebral edema.

### 8.14.4 Summary

Over the last three decades, consistent mortality reduction in subsets of liver failure not attributable to transplantation has been evident. Death from cerebral edema and brain herniation in ALF has also significantly decreased. There is not a defining therapeutic intervention that's has resulted in this



change. Perhaps this is the net result of improved and nuanced critical care delivery and the enhanced recognition of how dysfunction of other organ systems and their respective interventions affect cerebral metabolic and hemodynamic physiology.

## 8.15 Review Questions

**Question:** Plasma NH<sub>3</sub> level has to exceed 150 mmol/L in ALF before they are at risk of developing intracranial hypertension. **True or False ?**

**Answer: False**

An elevated plasma ammonia level (>150 mmol/L) in acute liver failure increases the risk of intracranial hypertension; however, a low level (<146 mmol/L) does not preclude it when associated with multiorgan failure. Vasogenic edema from hyperperfusion of the brain can occur independently of an elevated plasma ammonia levels due to the cytokine storm produced by the dying liver.

**Question:** Brain imaging for evaluating severe hepatic encephalopathy in patients with Acute-on-chronic Liver failure is unnecessary. **True or False ?**

**Answer:** Acute-on-chronic liver failure patients admitted with overt hepatic encephalopathy have a significantly higher short-term mortality rate and small but devastating risk of brain herniation (4%) and are at an increased risk of intracranial hemorrhage (16%). Atypical presentation of HE in these patients may warrant a head CT. In chronic liver disease without acute multiorgan failure, the yield from neuroimaging is low unless features are very atypical or there is a history of trauma.

**Question:** Hyperammonemia in chronic liver failure causes worsening encephalopathy leading to coma, however, the effect on the brain is always reversible with treatment. **True or False ?**

**Answer: False**

Ammonia is neurotoxic however patients with cirrhosis have a relative tolerance to hyperammonemia. Severe and sustained hyperammonemia in cirrhosis can cause irreversible brain injury akin to patients with urea cycle disorders. The threshold at which the injury is irreversible remain unclear. Brain MRI pattern of restricted diffusion (cytotoxic edema) in hyperammonemia states correlates in severity with plasma ammonia levels and clinical outcome.

**Question:** Induced hypothermia improves outcome in ALF by controlling ICP? **True or False ?**

**Answer: False**

Therapeutic hypothermia controls ICP, reduces plasma ammonia levels and is safe but does not confer a clear mortality benefit in acute liver failure.

**Question:** Monitoring and treating ICP in ALF using invasive intracranial monitoring devices result in improved control in ICP with a clear evidence of mortality benefit.

**True or False ?**

**Answer: False**

Invasive intracranial pressure monitoring used in an estimate of 20–30% of patients with acute liver failure in North America yields a 2.5–10% risk of intracranial hemorrhage. Patient's with intracranial monitors in a retrospective review received more interventions for ICP control and increased sedation without a discernable mortality benefit.

## References

1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35(3):716–21.
2. American Association for the Study of Liver D. European Association for the Study of the L: Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;61(3):642–59.
3. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. *Hepatology*. 1995;21(1):240–52.
4. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137(12):947–54.
5. O'Grady J. Modern management of acute liver failure. *Clin Liver Dis*. 2007;11(2):291–303.
6. Bernal W, Hyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol*. 2013;59(1):74–80.
7. Arroyo V, Moreau R, Jalan R, Gines P, Study E-CCC. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *J Hepatol*. 2015;62(1 Suppl):S131–43.
8. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrif L, Hopf C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology*. 2015;62(1):243–52.
9. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *J Hepatol*. 2015;62(2):437–47.
10. Donovan JP, Schafer DF, Shaw BW Jr, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. *Lancet*. 1998;351(9104):719–21.
11. Jalan R, Bernau J. Induction of cerebral hyperemia by ammonia plus endotoxin: does hyperammonemia unlock the blood-brain barrier? *J Hepatol*. 2007;47(2):168–71.
12. Jalan R, Dabos K, Redhead DN, Lee A, Hayes PC. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol*. 1997;27(5):928–33.

13. Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. *Liver Int.* 2014;34(3):362–6.
14. Zieve L. Pathogenesis of hepatic encephalopathy. *Metab Brain Dis.* 1987;2(3):147–65.
15. Albrecht J, Jones EA. Hepatic encephalopathy: molecular mechanisms underlying the clinical syndrome. *J Neurol Sci.* 1999;170(2):138–46.
16. Thumburu KK, Taneja S, Vasishta RK, Dhiman RK. Neuropathology of acute liver failure. *Neurochem Int.* 2012;60(7):672–5.
17. Raghavan M, Marik PE. Therapy of intracranial hypertension in patients with fulminant hepatic failure. *Neurocrit Care.* 2006;4(2):179–89.
18. Nguyen JH. Blood-brain barrier in acute liver failure. *Neurochem Int.* 2012;60(7):676–83.
19. Desjardins P, Du T, Jiang W, Peng L, Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure: role of glutamine redefined. *Neurochem Int.* 2012;60(7):690–6.
20. Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. *J Clin Exp Hepatol.* 2015;5(Suppl 1):S96–S103.
21. Ott P, Vilstrup H. Cerebral effects of ammonia in liver disease: current hypotheses. *Metab Brain Dis.* 2014;29(4):901–11.
22. Cordoba J, Blei AT. Brain edema and hepatic encephalopathy. *Semin Liver Dis.* 1996;16(3):271–80.
23. Wright G, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. *Liver Int.* 2011;31(2):163–75.
24. Karim Z, Szutkowska M, Vernimmen C, Bichara M. Renal handling of NH<sub>3</sub>/NH<sub>4</sub><sup>+</sup>: recent concepts. *Nephron Physiol.* 2005;101(4):77–81.
25. Olde Damink SW, Dejong CH, Deutz NE, Redhead DN, Hayes PC, Soeters PB, Jalan R. Kidney plays a major role in ammonia homeostasis after portosystemic shunting in patients with cirrhosis. *Am J Physiol.* 2006;291(2):G189–94.
26. Olde Damink SW, Jalan R, Deutz NE, Redhead DN, Dejong CH, Hynd P, Jalan RA, Hayes PC, Soeters PB. The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis. *Hepatology.* 2003;37(6):1277–81.
27. Tofteng F, Hauerberg J, Hansen BA, Pedersen CB, Jorgensen L, Larsen FS. Persistent arterial hyperammonemia increases the concentration of glutamine and alanine in the brain and correlates with intracranial pressure in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab.* 2006;26(1):21–7.
28. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology.* 1999;29(3):648–53.
29. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology.* 2007;46(6):1844–52.
30. Scott TR, Kronsten VT, Hughes RD, Shawcross DL. Pathophysiology of cerebral oedema in acute liver failure. *World J Gastroenterol.* 2013;19(48):9240–55.
31. Orman ES, Perkins A, Ghabril M, Khan BA, Chalasani N, Boustani MA. The confusion assessment method for the intensive care unit in patients with cirrhosis. *Metab Brain Dis.* 2015;30(4):1063–71.
32. Conn H, Bircher J. Quantifying the severity of hepatic encephalopathy. Bloomington, IL: Medi-Ed Press; 1994.
33. Wijdsicks EF. Hepatic Encephalopathy. *N Engl J Med.* 2016;375(17):1660–70.
34. Ortiz M, Cordoba J, Doval E, Jacas C, Pujadas F, Esteban R, Guardia J. Development of a clinical hepatic encephalopathy staging scale. *Aliment Pharmacol Ther.* 2007;26(6):859–67.
35. Conn H. Portal-systemic encephalopathy (PSE) after transjugular intrahepatic portal-systemic stent-shunts (TIPS). *Ital J Gastroenterol.* 1993;25(7):397–9.
36. Bernal W, Wendon J. Acute liver failure. *N Engl J Med.* 2014;370(12):1170–1.
37. Hobbs K, Stern-Nezer S, Buckwalter MS, Fischbein N, Finley Caulfield A. Metronidazole-induced encephalopathy: not always a reversible situation. *Neurocrit Care.* 2015;22(3):429–36.
38. Kato H, Sosa H, Mori M, Kaneko T. Clinical characteristics of metronidazole-induced encephalopathy: a report of two cases and a review of 32 Japanese cases in the literature. *Kansenshogaku Zasshi.* 2015;89(5):559–66.
39. Sandip S, Afshan I, Khandelwal RK. MR features of metronidazole-induced encephalopathy. *BMJ Case Rep.* 2015;2015:bcr2015212609.
40. Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, Angeli P, Domenicali M, Gines P, Bernardi M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). *J Hepatol.* 2014;60(2):275–81.
41. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database Syst Rev.* 2004;2:CD003044.
42. Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L, Gil S, Garcia-Ramos G. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. *Hepatology.* 1987;7(4):639–43.
43. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology.* 1977;72(4 Pt 1):573–83.
44. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, de Sa MF. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. *Hepatogastroenterology.* 1992;39(6):542–5.
45. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. *Gut.* 1982;23(1):1–7.
46. Chavez-Tapia NC, Cesar-Arce A, Barrientos-Gutierrez T, Villegas-Lopez FA, Mendez-Sanchez N, Uribe M. A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. *Nutr J.* 2013;12:74.
47. Timbol AB, Razo RI, Villaluna RA, Ong J. 740: Zinc supplementation for hepatic encephalopathy in chronic liver disease: a meta-analysis. *Crit Care Med.* 2013;41(12):A183.
48. Corvi MM, Soltys CL, Berthiaume LG. Regulation of mitochondrial carbamoyl-phosphate synthetase L1 activity by active site fatty acylation. *J Biol Chem.* 2001;276(49):45704–12.
49. Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, Sherwood R, Wendon JA, Bernal W. Ammonia clearance with haemofiltration in adults with liver disease. *Liver Int.* 2014;34(1):42–8.
50. Cordoba J, Blei AT, Mujais S. Determinants of ammonia clearance by hemodialysis. *Artif Organs.* 1996;20(7):800–3.
51. Chawla R, Smith D, Marik PE. Near fatal posterior reversible encephalopathy syndrome complicating chronic liver failure and treated by induced hypothermia and dialysis: a case report. *J Med Case Reports.* 2009;3:6623.
52. Whitelaw A, Bridges S, Leaf A, Evans D. Emergency treatment of neonatal hyperammonaemic coma with mild systemic hypothermia. *Lancet.* 2001;358(9275):36–8.
53. Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database Syst Rev.* 2004;2:CD002798.
54. Lynn AM, Singh S, Congly SE, Khemani D, Johnson DH, Wiesner RH, Kamath PS, Andrews JC, Leise MD. Embolization of

- portosystemic shunts for treatment of medically refractory hepatic encephalopathy. *Liver Transpl.* 2016;22(6):723–31.
55. Keays R, Potter D, O'Grady J, Peachey T, Alexander G, Williams R. Intracranial and cerebral perfusion pressure changes before, during and immediately after orthotopic liver transplantation for fulminant hepatic failure. *Q J Med.* 1991;79(289):425–33.
  56. Yan S, Tu Z, Lu W, Zhang Q, He J, Li Z, Shao Y, Wang W, Zhang M, Zheng S. Clinical utility of an automated pupillometer for assessing and monitoring recipients of liver transplantation. *Liver Transpl.* 2009;15(12):1718–27.
  57. Kitzberger R, Funk GC, Holzinger U, Miehsler W, Kramer L, Kaider A, Ferenci P, Madl C. Severity of organ failure is an independent predictor of intracranial hypertension in acute liver failure. *Clin Gastroenterol Hepatol.* 2009;7(9):1000–6.
  58. Wijedicks EF, Plevak DJ, Rakela J, Wiesner RH. Clinical and radiologic features of cerebral edema in fulminant hepatic failure. *Mayo Clin Proc.* 1995;70(2):119–24.
  59. Munoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B, Martin P, Maddrey WC. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology.* 1991;13(2):209–12.
  60. Thayaparaiah SW, Gulka I, Al-Amri A, Das S, Young GB. Acute fulminant hepatic failure, encephalopathy and early CT changes. *Can J Neurol Sci.* 2013;40(4):553–7.
  61. McKinney AM, Sarikaya B, Spanbauer J, Lohman BD, Uhlmann E. Acute hepatic (or hyperammonemic) encephalopathy: diffuse cortical injury and the significance of ammonia. *Am J Neuroradiol.* 2011;32(7):E142. author reply E143.
  62. JM U-K-I, Yu E, Bartlett E, Soobrah R, Kucharczyk W. Acute hyperammonemic encephalopathy in adults: imaging findings. *Am J Neuroradiol.* 2011;32(2):413–8.
  63. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E, Bernal W, Auzinger G, Shawcross D, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol.* 2016;64:69.
  64. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML, Group USALFS. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. *Liver Transpl.* 2015;21(1):4–12.
  65. Tapper EB, Jiang ZG, Patwardhan VR. Refining the ammonia hypothesis: a physiology-driven approach to the treatment of hepatic encephalopathy. *Mayo Clin Proc.* 2015;90(5):646–58.
  66. Citerio G, Vascotto E, Villa F, Celotti S, Pesenti A. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. *Crit Care Med.* 2001;29(7):1466–71.
  67. Polson J, Lee WM. American Association for the Study of Liver D: AASLD position paper: the management of acute liver failure. *Hepatology.* 2005;41(5):1179–97.
  68. Larsen FS, Hansen BA, Ejlersen E, Secher NH, Clemmesen JO, Tygstrup N, Knudsen GM. Cerebral blood flow, oxygen metabolism and transcranial Doppler sonography during high-volume plasmapheresis in fulminant hepatic failure. *Eur J Gastroenterol Hepatol.* 1996;8(3):261–5.
  69. Scheuermann K, Thiel C, Thiel K, Klingert W, Hawerkamp E, Scheppach J, Konigsrainer A, Morgalla MH, Leckie P, Proven A, et al. Correlation of the intracranial pressure to the central venous pressure in the late phase of acute liver failure in a porcine model. *Acta Neurochir Suppl.* 2012;114:387–91.
  70. Keays RT, Alexander GJ, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. *J Hepatol.* 1993;18(2):205–9.
  71. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, Han S, Harrison ME, Stravitz TR, Munoz S, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl.* 2005;11(12):1581–9.
  72. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet.* 1993;341(8838):157–8.
  73. Lidofsky SD, Bass NM, Prager MC, Washington DE, Read AE, Wright TL, Ascher NL, Roberts JP, Scharschmidt BF, Lake JR. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology.* 1992;16(1):1–7.
  74. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, Group USALFS. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. *Crit Care Med.* 2014;42(5):1157–67.
  75. Kositchaiwat C, Chuansumrit A. Experiences with recombinant factor VIIa for the prevention of bleeding in patients with chronic liver disease undergoing percutaneous liver biopsies and endoscopic retrograde cholangiopancreatography (ERCP). *Thromb Haemost.* 2001;86(4):1125–6.
  76. Shami VM, Caldwell SH, Hespeneide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl.* 2003;9(2):138–43.
  77. Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer JF 2nd. Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. *Liver Transpl.* 2008;14(7):1048–57.
  78. Abdo A, Lopez O, Fernandez A, Santos J, Castillo J, Castellanos R, Gonzalez L, Gomez F, Limonta D. Transcranial Doppler sonography in fulminant hepatic failure. *Transplant Proc.* 2003;35(5):1859–60.
  79. Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology.* 2004;39(2):464–70.
  80. Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut.* 1982;23(7):625–9.
  81. Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care.* 2004;1(2):219–33.
  82. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med.* 2010;38(5):1348–59.
  83. Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. *Dan Med Bull.* 2007;54(2):99–111.
  84. Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol.* 1986;2(1):43–51.
  85. Forbes A, Alexander GJ, O'Grady JG, Keays R, Gullan R, Dawling S, Williams R. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology.* 1989;10(3):306–10.
  86. Jalan R, Olde Damink SW, Deutz NE, Lee A, Hayes PC. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet.* 1999;354(9185):1164–8.
  87. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology.* 2004;127(5):1338–46.
  88. Vaquero J. Therapeutic hypothermia in the management of acute liver failure. *Neurochem Int.* 2012;60(7):723–35.
  89. Larsen F.S. Murphy N, Bernal W, Bjerring PN, Hauerberg J, Wendon J., 2011 EUROALF Group. The prophylactic effect of mild hypothermia to prevent brain edema in patients with acute liver failure: results of a multicenter randomized, controlled trial (abstract). *J Hepatol.* 54(Suppl 1):S26.

90. Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab.* 2004;24(7):798–804.
91. Ellis AJ, Wendon JA, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. *Hepatology.* 2000;32(3):536–41.
92. Bhatia V, Batra Y, Acharya SK. Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure--a controlled clinical trial. *J Hepatol.* 2004;41(1):89–96.
93. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit Care Med.* 1993;21(3):328–38.
94. William M. Lee, AM Larson, R. Todd Stravitz. AASLD Position paper: the management of acute liver failure: update 2011. 2011.

## Further Readings

- Bernal W, Wendon J. Acute liver failure. *N Engl J Med.* 2014;370(12):1170–1.
- Bernal W, Hyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol.* 2013;59(1):74–80.
- Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. *Liver Int.* 2014;34(3):362–6.
- Wijdicks EF. Hepatic encephalopathy. *N Engl J Med.* 2016;375(17):1660–70.
- Al-Khafaii A, editor. ICU care of abdominal organ transplant patients. 1st ed. Oxford: Oxford University Press; 2013.



Sukhjeet Singh and Steven M. Hollenberg

## Abstract

The liver and heart are closely related in health and in disease; the liver receives 25 to 30% of total cardiac output via the hepatic artery, and the portal vein. Liver disease can result from right-sided heart failure, with manifestations ranging from mild reversible liver injury to hepatic fibrosis, and, in its most severe form, cardiac cirrhosis. On the other end of the spectrum, advanced liver disease can manifest itself as a hyperdynamic state with decreased vascular resistance, but with concomitant cardiac dysfunction that is termed cirrhotic cardiomyopathy. The degree of cardiac derangement correlates with the degree of liver dysfunction, and may lead to other disease processes such as hepatorenal syndrome and hepatic encephalopathy. Prompt recognition and treatment of the underlying cause of acute decompensation is the only definitive therapy for this devastating disease process.

## Keywords

Cirrhotic cardiomyopathy • Hyperdynamic state • Acute liver failure • Acute on chronic liver failure • Echocardiography

## Abbreviations

ALF	acute liver failure
ACLF	acute on chronic liver failure
ANP	atrial natriuretic peptide
BNP	B-type natriuretic peptide
CCM	cirrhotic cardiomyopathy
CLF	chronic liver failure
CLIF	chronic liver failure organ failure
CMR	cardiac magnetic resonance imaging
CO	cardiac output
HF	heart failure
HTN	hypertension
ICU	intensive care unit
LT	liver transplant
NO	nitric oxide

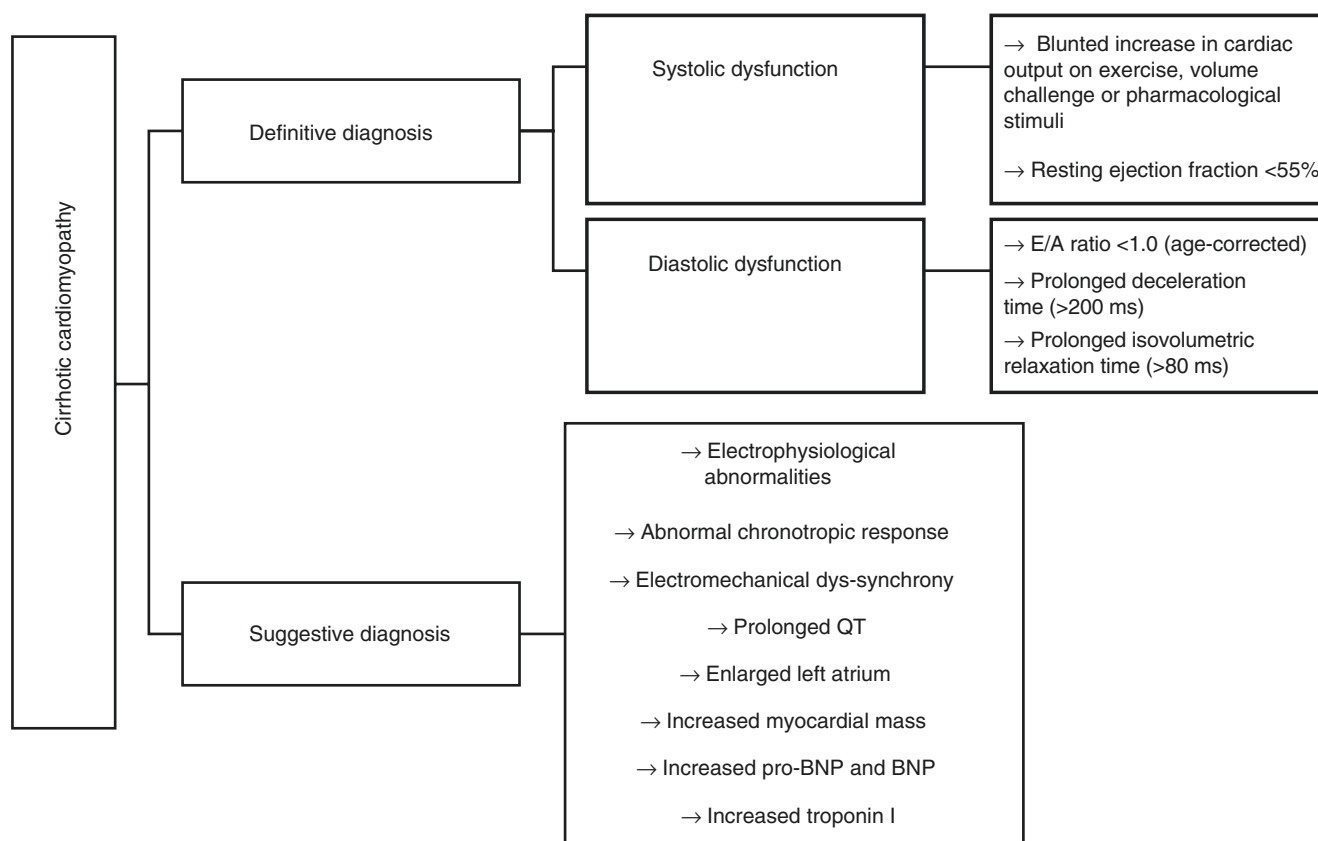
NOS	nitric oxide synthase
SPECT	single photon emission computed tomography
SVR	systemic vascular resistance
TIPS	transjugular intrahepatic portosystemic shunt

## 9.1 Introduction

The circulatory system is a complex mechanism to provide adequate blood supply to multiple organs in the body. The liver and heart are closely related in health and in disease; the liver receives 25–30% of total cardiac output via the hepatic artery, and the portal vein. The portal vein supplies nutrient-rich blood from the mesenteric and splenic veins, and provides 70% of the hepatic blood flow. The portal vein does not have the ability to autoregulate its flow, which is primarily dependent on mesenteric circulation, and the gradient between the portal and hepatic venous pressures [1]. The remainder of the metabolic demands of the liver are met by the hepatic artery, a branch of the celiac trunk. In consequence, liver disease can result from right-sided heart

S. Singh, D.O., J.D. • S.M. Hollenberg, M.D. (✉)  
Department of Cardiovascular Disease, Cooper University  
Hospital, Camden, NJ, USA  
e-mail: [Hollenberg-steven@cooperhealth.edu](mailto:Hollenberg-steven@cooperhealth.edu)





**Fig. 9.1** Diagnostic and supportive criteria for cirrhotic cardiomyopathy

failure, with manifestations ranging from mild reversible liver injury to hepatic fibrosis, and, in its most severe form, cardiac cirrhosis [2]. On the other end of the spectrum, advanced liver disease can manifest itself as a hyperdynamic state with decreased vascular resistance, but with concomitant cardiac dysfunction that is termed cirrhotic cardiomyopathy [3].

The dual blood supply of the liver and its high metabolic activity make it particularly vulnerable to circulatory disturbances. There are many well-known entities of vascular injury to the liver, including Budd-Chiari Syndrome, hepatic sinusoidal obstruction, ischemic hepatitis, and cardiac cirrhosis. **Cardiac cirrhosis** (congestive hepatopathy) includes a spectrum of disorders related to elevated central venous pressures, but most often results from chronic heart failure. Cardiac cirrhosis is a chronic condition in which elevated central venous pressures from processes such as constrictive pericarditis, cardiomyopathies, and tricuspid and pulmonic valve disease cause liver congestion; hepatic function deteriorates slowly, and cardiac cirrhosis permits long-term survival. **Ischemic hepatitis** is the result of diffuse hepatic injury from acute hypoperfusion. The diagnosis of ischemic hepatitis requires a clinical scenario consistent with reduced oxygen delivery or metabolism by the liver, elevation of serum aminotransferases, and exclusion of other causes of liver injury such as drug exposure or viral hepatitis [4]. It is of paramount importance to distinguish right-sided heart

failure leading to cardiac cirrhosis from left sided heart failure which results in ischemic hepatitis [5].

**Cirrhotic cardiomyopathy** is defined as chronic cardiac dysfunction in patients with liver failure related to impaired cardiac contractility in response to stress in cirrhotic patients with no known underlying cardiac disorders [6, 7]. Altered diastolic relaxation and electrophysiological abnormalities may be present as well [7]. Originally cardiac impairment due to hyperdynamic circulation was termed “high output heart failure” [3, 8]. An autopsy series showed cardiomyocyte edema and cardiac hypertrophy in subjects with cirrhosis without evidence of coronary artery disease, hypertension, or valvular disease [9]. More recently, diagnostic and supportive criteria for cirrhotic cardiomyopathy were proposed by an expert conference in 2005 [7]. These criteria are listed in Fig. 9.1.

Data regarding the prevalence of cirrhotic cardiomyopathy are limited, because cardiac function is usually normal at rest. It is only during periods of stress that cardiac dysfunction is unmasked and symptoms of fatigue, edema, and decreased exercise tolerance may become manifest. Such symptoms may also be related to the underlying liver disease, complicating the diagnosis of cirrhotic cardiomyopathy [10, 11]. It has been postulated that as many as 50% of patients undergoing liver transplant have some degree of underlying cardiac dysfunction [11], and death from heart failure in the post liver transplantation period is estimated to be 7–21% [12].

## 9.2 Pathophysiology

The liver is the largest organ in the human body and a primary component of the reticuloendothelial system. Normally the liver is a high compliance and low resistance organ that can accommodate large volumes of blood without an increase in portal pressure. The functional unit of the liver has been described using two models: the classic lobule and the liver acinus [13, 14]. The hepatic lobule is the structural and functional unit of the liver [15]. It is a hexagonal structure composed of one cell thick by 15–25 hepatocytes in length around a central venule, a branch of the hepatic vein. The portal tracts consist of hepatic artery, portal vein, bile ducts, lymphatics, and nerves, located at the corners of the hexagon. The liver acinus describes the liver parenchyma in zones related to arterial perfusion. Zone 1 hepatocytes are the closest to the triad, and receive the richest supply of oxygen and nutrients. However, due to their close proximity, zone 1 hepatocytes are also likely to be exposed to drugs and toxins at high concentrations. The hepatocytes in zone 3 are near the central vein and have a poor supply of oxygen. These hepatocytes are more likely to suffer from hypoxia and venous congestion. Different pathologies affect different portions of the liver lobule.

The most common cause of acute liver injury due to heart disease is ischemic hepatitis, also termed “shock liver,” or “hypoxic hepatitis” [16]. A reduction in cardiac output results in decreased hepatic arterial perfusion and centrilobular necrosis in liver zone 3. Concomitant congestive heart failure leads to increased central venous pressure and central hypoxia [17]. Cardiac cirrhosis, on other hand, is a disease in which elevated central venous pressures which leads to hepatic sinusoidal dilation, sinusoidal edema, and sinusoidal hypertension. These events cause progressive zone 3 hepatocyte hypertrophy, centrilobular fibrosis, portal hypertension, and ascites. As the sinusoidal fenestrae enlarge, hepatocyte necrosis becomes more prominent, resulting in leakage of protein rich fluid through the lymphatics [5]. The extent of fibrosis is variable, and may be dependent on local fibrogenic effects of thrombi within the sinusoids, hepatic venules, and portal veins [18].

Liver function tests provide accurate and timely identification of liver disease. Significant hepatocellular injury or necrosis is reflected in elevation of circulating levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), enzymes that are present in hepatocytes. Obstructive or cholestatic disease can result in elevations in bilirubin or alkaline phosphatase. Impaired hepatic synthetic function may be manifested by low albumin and decreased clotting factor production, and is reflected by prolonged prothrombin time [19–21].

Liver failure is a hyperdynamic state resulting in increased cardiac output and decreased or near normal blood pressure. The primary mechanism behind this hyperdynamic circulation is peripheral and splanchnic vasodilation, along with portal hypertension [22]. Several humoral mediators have

been identified that lead to systemic vasodilation: nitric oxide, adrenomedullin, natriuretic peptides, cytokines, hydrogen sulfide, endothelins, and endocannabinoids [23, 24]. The most important of these factors is nitric oxide (NO), which was hypothesized to be a critical factor in the splanchnic vasodilation in cirrhosis and portal hypertension more than 20 years ago [25]. NO has a very short half-life (20–30 s), can diffuse readily across the cell membrane, and acts primarily by upregulating the production of cyclic-GMP by guanylate cyclase, with resultant smooth muscle relaxation. NO bioavailability is increased in patients with cirrhosis and portal hypertension due to increased activity of nitric oxide synthase (NOS) [26]. There are three known isoforms of NOS: neuronal (nNOS), inducible (iNOS), and endothelial (eNOS). It has been hypothesized that cirrhosis results in increased levels of circulating cytokines, which causes induction of iNOS and overproduction of NO [27].

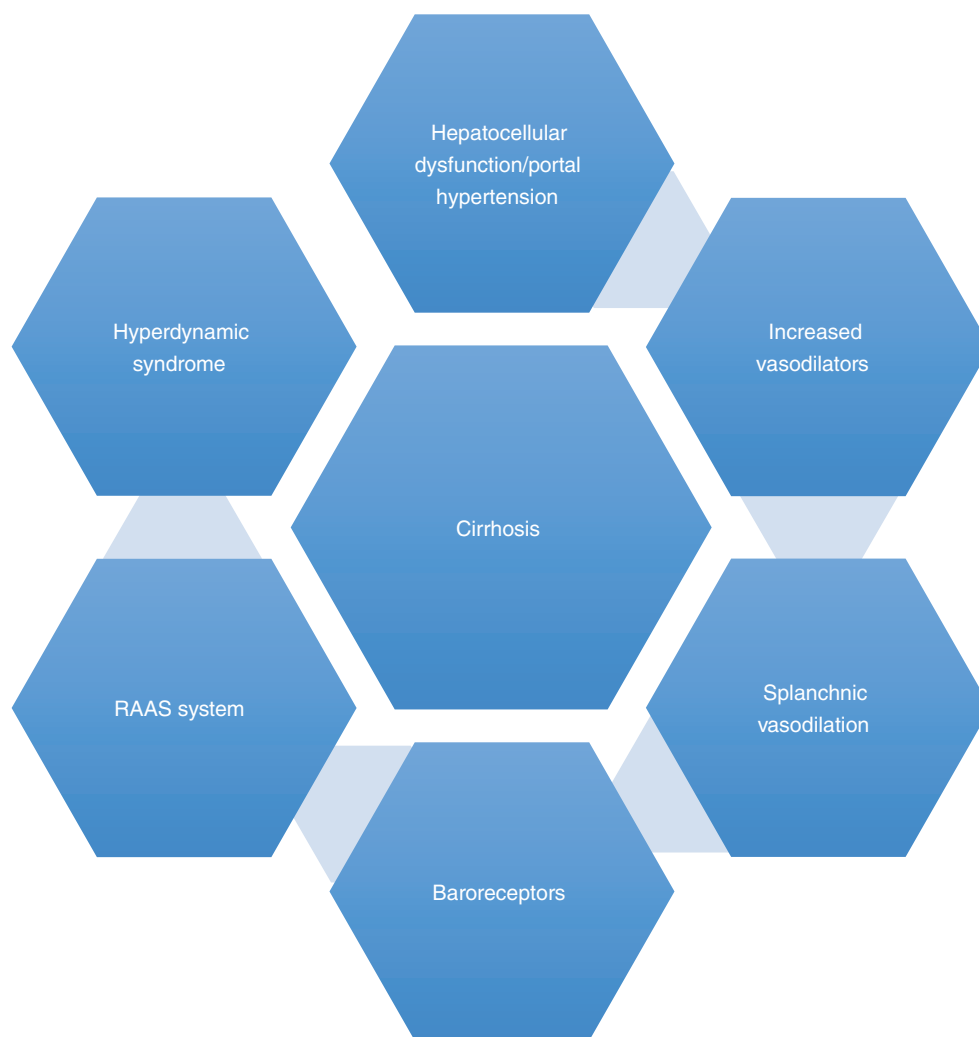
Elevated levels of NO cause smooth muscle relaxation resulting in splanchnic and mesenteric vasodilation. Dilation of peripheral arteries is sensed by the baroreceptors as a decrease in effective circulating blood volume. This in turn activates the renin-angiotensin-aldosterone system and retention of salt and water. These events further increase cardiac preload and cardiac output. Besides vasodilation NO also decreases the vascular response to vasoconstrictors [28]. In patients with cirrhosis, elevated cardiac output is independently associated with higher hepatic blood flow and increased hepatic venous pressure gradient [29]. Long term use of NOS inhibitors in ascitic cirrhotic rats completely normalized the parameters of hyperdynamic circulation [30].

Alongside vasoactive substances, formation of portosystemic shunts also increases systemic circulatory flow. In patients with cirrhosis, portal pressure rises, resulting in reversal of blood flow within the portal vein. As the hepatic venous pressure gradient exceeds 10 mmHg, extensive collateral formation between the portal system and splanchnic system ensues. Collateral circulation increases hyperdynamic circulation by directly reducing peripheral resistance, and by allowing vasoactive substances to bypass the liver and reach systemic circulation [31]. The most clinically relevant of these collaterals are gastroesophageal varices, which are present in almost half of the patients with cirrhosis [32] (Fig. 9.2).

### 9.2.1 Acute Liver Failure as a Cause of Cardiac Dysfunction

*Acute liver failure (ALF)* is defined as concurrent appearance of hepatic encephalopathy and coagulation abnormalities in the setting of acute liver dysfunction of any kind, and in the absence of pre-existing liver disease [33]. The designation *acute liver failure* has replaced older terms such as fulminant hepatic failure, hyperacute liver failure, and subacute liver failure. Patients with hyperacute liver failure

**Fig. 9.2** Mechanisms leading to hyperdynamic circulation and ascites in patient with cirrhosis. Portal hypertension leads to formation of collaterals and splanchnic arterial vasodilation. Systemic vasodilation is mediated by a number of circulating substances; primary among them is nitric oxide. Abnormal vasodilation leads to decrease in effective circulating volume and activation of baroreceptors. Neurohormonal pathways are activated, leading to an increase in renin-angiotensin-aldosterone and sympathetic nervous systems. This causes increased sodium and water retention, and further exacerbation of the hyperdynamic syndrome



were defined as development of encephalopathy within 7 days of onset of liver dysfunction, and generally have a better prognosis with medical management. Subacute liver failure is defined as development of encephalopathy within 5–26 weeks, usually with worse prognosis. ALF is a term that encompasses all forms of liver injury occurring up to 26 weeks after the initial insult [34, 35]. The leading cause of ALF in the developed world is acetaminophen and other drug usage [36]. In contrast, viruses are the leading cause of ALF in the developing world [37]. Although the clinical presentation of ALF is similar regardless of etiology, outcomes are dependent on etiology, and must be clarified for prognostic assessment [35].

All patients with clinical or laboratory evidence of acute hepatitis should have immediate measurement of prothrombin time and careful evaluation of mental status. If laboratory values reveal a prolonged prothrombin time by ~4–6 s or more,  $\text{INR} \geq 1.5$ , and any change in mental status from baseline, the diagnosis of ALF is made and hospital admission is mandatory. If patients develop grade I or II

**Table 9.1** Grades of hepatic encephalopathy

GRADE 1	Trivial lack of awareness Euphoria or anxiety
GRADE 2	Shortened attention span Lethargy or apathy Minimal disorientation to time or place Subtle personality change Inappropriate behavior
GRADE 3	Somnolence Responsive to verbal stimuli Confusion
GRADE 4	Coma

encephalopathy (Table 9.1), ICU transfer is warranted, along with a consultation to transplant center [38]. Careful history and physical examination should be performed to ascertain any viral or drug exposures. Physical examination may reveal fatigue, malaise, lethargy, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, or ascites [39]. Initial laboratory evaluation should be thorough in order to evaluate both the etiology and severity of ALF.

Computed tomography (CT) of the abdomen often reveals a liver that is denser than skeletal muscle, heterogeneous liver parenchyma, hepatomegaly, ascites, hepatic vein occlusion, and cirrhosis [40]. Head CT may reveal cerebral edema, decrease in the size of ventricles, and flattening of cerebral convolutions [41]. Approximately 30% of the patients with ALF will develop pulmonary edema and/or pulmonary infections, which may be seen on chest imaging [42]. Liver biopsy is indicated if imaging and laboratory data fail to reveal the cause of liver failure. Due to the underlying coagulopathy the transjugular approach is most often employed [38].

The pathogenic mechanism behind cardiac dysfunction in acute liver failure is hyperdynamic circulation. This is related to vasoactive substances and reduction in systemic vascular resistance which leads to hemodynamic and cardiovascular dysfunction. Despite adequate perfusion and adequate oxygen delivery, tissue uptake of oxygen is impaired, which leads to lactic acidosis [43]. Decreased clearance of lactate may also contribute to elevated serum levels. Additionally, adrenal insufficiency is present in about 60% of patients with ALF, which may contribute to hemodynamic compromise due to consequent dysfunction in the renin-angiotensin-aldosterone pathway [44]. Treatment of the underlying cause of ALF usually improves the cardiac and other organ dysfunction.

In adults, 25% of patients are transplanted, survival without transplantation is 45%, and mortality is 30% [45]. Cardiac insult in patients with ALF is usually reversible with liver transplantation. On the other hand, preexisting cardiac dysfunction prior to ALF is associated with worse outcomes after liver transplantation [46].

### 9.2.2 Chronic Liver Failure as Cause of Cardiac Dysfunction

Chronic liver failure is a disease process of the liver leading to fibrosis and cirrhosis. *Cirrhosis* represents the final state of chronic liver disease and occurs in response to chronic wound healing. Cirrhosis is characterized by distortion of the hepatic architecture and the formation of regenerative nodules [47]. The most common causes of cirrhosis in the United States are hepatitis C, alcoholic liver disease, and nonalcoholic liver disease, which accounted for 80% patients on the liver transplant between 2004 and 2013 [48]. Cirrhosis accounted for approximately 49,500 deaths and was the eleventh leading cause of death in the United States in 2010 [49].

The majority of the complications of cirrhosis result from portal hypertension and formation of venous collaterals. Most patients with chronic liver disease and moderate to severe liver injury have at least one characteristic finding of cirrhotic cardiomyopathy, such as systolic dysfunction, diastolic dysfunction, or electrocardiographic abnormalities. Diastolic dysfunction is present in an estimated 45–56% of patients with

cirrhotic cardiomyopathy [50]. The major pathophysiologic mechanisms of cirrhotic cardiomyopathy in chronic liver failure include impairment of stimulatory adrenergic receptor pathways [51, 52], nuclear and cytoplasmic vacuolation of cardiomyocytes, and alterations of cardiomyocyte membrane properties. In addition, there is overproduction of nitric oxide synthase, which leads to elevated levels of nitric oxide, which can have a negative inotropic effect on the heart [53, 54].

Cirrhosis is generally considered to be an irreversible phenomenon, even though the exact time at which it becomes irreversible is unclear [55]. The primary goal of management of patients with cirrhosis include slowing the progression of liver disease, preventing further superimposed injury, adjusting doses of medications, and determining the appropriateness and optimal timing of liver transplant. Targeted therapies against the underlying cause of cirrhosis should be initiated to halt the progression of the disease. For example, patients with hepatitis C and cirrhosis who are treated with antiviral treatment and have a sustained virologic response have a lower liver-related mortality than those patients who do not achieve sustained virologic response [56]. In alcoholic cirrhosis, abstinence from alcohol improves survival [57], improvement in fibrosis [58], reduction of portal pressures [59], and resolution of ascites [60].

## 9.3 Evaluation of Cardiac Dysfunction in Liver Disease

Cardiac dysfunction in liver disease has been described since the 1960. Prior to that, cardiac dysfunction was often attributed erroneously to alcoholic cardiomyopathy [3, 61]. In the past two decades two important entities have emerged as the predominant processes involved in with the heart and the liver: cardiac cirrhosis and cirrhotic cardiomyopathy. Cardiac cirrhosis, also named *congestive hepatopathy*, is liver dysfunction secondary to chronically elevated right sided central pressures. It is of paramount importance to distinguish cardiac cirrhosis from cirrhotic cardiomyopathy and to delineate the severity of right heart failure, because optimal treatment of liver failure is dependent on the treatment of underlying heart failure. The first step is echocardiography, which can evaluate the size and function of right heart chambers, and derive an estimate of right ventricular and pulmonary artery systolic pressures [62].

Cirrhotic cardiomyopathy is primarily characterized by a blunted cardiac response to stress or exercise, which suggests underlying cardiac processes. Over the last 20 years, it has been shown that the underlying cardiac dysfunction may even precede other well-known complications of cirrhosis, such as hepatorenal syndrome [63]. Because the circulation in patients with cirrhosis may be hyperdynamic secondary to increased preload and reduced afterload, LV systolic func-

tion at rest may be normal or increased, potentially leading to a false assumption of normal cardiac function. Normally, during periods of stimuli such as exercise or stress, cardiac output and contractility increases from baseline to meet the metabolic demands. However, due to reduced myocardial reserve, impaired oxygen extraction, and blunted heart rate response the cardiac apparatus may not be able to meet the metabolic demands [64]. On the other hand, if cardiac reserve is defined as a percentage increase with stress, and cardiac output is increased in liver failure compared to normal patients, then an increase in liver failure to the same absolute cardiac output as normal will result in a lower percentage increase. For this reason, a measurement of decreased cardiac reserve in liver failure must be accompanied by clinical manifestations of decreased exercise tolerance or an inadequate response to physiologic stress.

Diastolic dysfunction may be a component of cirrhotic cardiomyopathy as well. Diastolic dysfunction leads to impaired filling of the LV during diastole, hindering the ability of the LV to adequately raise stroke volume in response to stress or exercise. Diastolic dysfunction may precede systolic dysfunction, and may represent the earliest manifestation of cirrhotic cardiomyopathy [65]. Additionally, the degree of diastolic dysfunction was shown to have a strong correlation with the degree of liver failure at 2 year follow-up [10, 66]. In cirrhosis, a decreased preload reserve response has been reported in both human [67] and animal models [68]. A decrease in preload response occurs when cardiac output fails to increase after an increase in preload. In these studies, cardiac output was increased at baseline secondary to decreased peripheral vascular resistance and failed to increase with volume challenge. This reduced preload response may be a result of cardiac hypertrophy, patchy fibrosis, and sub-endothelial edema [7].

Electrophysiological abnormalities are well documented in patient with cirrhosis, with the prevalence of QT prolongation exceeding 60% in patients with advanced cirrhosis [69]. Studies in rats with cirrhosis suggest that these QT prolongation abnormalities are caused by potassium channel alterations and decreased plasma membrane fluidity [70, 71]. QT prolongation is partially reversible via the use of  $\beta$ -blocker therapy [72], although the indication for their use in patients with cirrhosis is portal hypertension, not electrophysiological abnormalities [73]. Additionally, these abnormalities disappear after liver transplant [74, 75].

Chronotropic incompetence to exercise and other stimuli has also been observed in patients with cirrhosis. Though patients with cirrhosis are frequently tachycardic secondary to elevated levels of circulating catecholamines, one hallmark of the disease is the failure to increase heart rate to maintain adequate cardiac output during times of increased metabolic demand [76]. The exact clinical importance of chronotropic incompetence in cirrhotic

patients is unknown; however, recent studies suggest failure to increase heart rate adequately may play a role in paracentesis-induced circulatory failure [77], renal failure precipitated by spontaneous bacterial peritonitis [78], and hepato-renal syndrome [79].

### 9.3.1 Diagnosis

*Clinical symptoms* of overt heart failure may be absent due to peripheral vasodilation and afterload reduction in patients with liver cirrhosis. Moreover, symptoms of dyspnea, fatigue, fluid retention, ascites, weight loss, and reduced exercise capacity are difficult to distinguish from the underlying liver disease. The presence of hydrothorax from direct extension of ascites into the pleural cavity or large amounts of ascites in the absence of pre-existing right heart failure suggests a hepatic cause. On the other hand, pulmonary congestion strongly suggests a cardiac cause [50]. Cirrhosis should be suspected in patients with jaundice, spider angiomas, gynecomastia, ascites, splenomegaly, palmar erythema, digital clubbing, and asterixis [80].

Small changes in intravascular volumes can have profound effects on diastolic indices in liver disease. Diastolic function is measured using Doppler echocardiography. One measure of diastolic function on echocardiography is the ratio of early mitral filling velocity (E) to the velocity with the atrial kick (A), the E/A ratio. The E/A ratio is decreased in cirrhotic patients, especially in those with ascites. Furthermore, studies have shown an improvement in E/A ratio after paracentesis [10, 81]. Although E/A is a measure of diastolic function, it is highly dependent on preload conditions. Doppler tissue velocity ( $E'$ ), which measures slow velocity high amplitude mitral annular tissue motion, is less affected by preload, and is a more sensitive measure of diastolic dysfunction [82]. Diagnostic evaluation of systolic and diastolic dysfunction in patients with cirrhosis is summarized in Table 9.2.

**Table 9.2** Diagnostic evaluation of systolic and diastolic function

Systolic dysfunction	Diastolic dysfunction
<ul style="list-style-type: none"> <li>• Echocardiography/MRI               <ul style="list-style-type: none"> <li>• Volumes</li> <li>• Ejection fraction</li> <li>• Response to stress (dobutamine)</li> <li>• Wall motion</li> </ul> </li> <li>• Exercise ECG               <ul style="list-style-type: none"> <li>• Exercise capacity</li> <li>• Oxygen consumption</li> </ul> </li> <li>• Radionuclide angiography/Myocardial perfusion Imaging               <ul style="list-style-type: none"> <li>• Ejection fraction</li> <li>• Cardiac volumes</li> <li>• Wall motion and thickening</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Echocardiography/MRI               <ul style="list-style-type: none"> <li>• E/A ratio</li> <li>• Deceleration time</li> <li>• Relaxation time</li> </ul> </li> </ul>



**Table 9.3** Initial laboratory evaluation for liver disease

• Chemistries
• Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, creatinine, blood urea nitrogen
• AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin
• Arterial blood gas
• Lactate
• Complete blood count
• Prothrombin time/INR
• Blood type and screen
• Acetaminophen level
• Urine drug screen
• Viral hepatitis serologies
• HAV, HBV, HCV
• Ceruloplasmin level if there is suspicion for Wilson's disease
• Pregnancy test
• Autoimmune markers
• ANA, immunoglobulin levels, anti-smooth muscle antibodies (autoimmune hepatitis)
• HIV 1 and 2 screen
• Amylase and lipase

*Laboratory* examination needs to be extensive in order to evaluate precipitating factors and the extent of the disease (for a list of recommended laboratory tests, see Table 9.3). These should include basic chemistries, hepatic synthetic panel, viral panel, alcohol, and acetaminophen and other drug ingestions. Cardiac cirrhosis values generally reveal a cholestatic pattern with increased alkaline phosphatase and mild elevation in bilirubin levels [83]. Serum aminotransferase levels are elevated in about a third of the patients, but usually no more than two or three times the upper limit of normal. Ischemic hepatitis, however, presents with severely elevated bilirubin levels as high as 15–20 mg/dL, and serum aminotransferase levels more than ten times the upper normal limit [19]. See Table 9.4 for a comparison of laboratory findings in acute ischemic hepatitis and cardiac cirrhosis.

### 9.3.2 Biomarkers

Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and cardiac troponin are molecular biomarkers that have been studied in patients with liver disease and LV dysfunction. ANP is a peptide synthesized by the cardiac atria and secreted in response to increased intravascular volume and LV hypertrophy. As a result of hyperdynamic circulation, levels of ANP are usually elevated in patients with cirrhosis and ascites [84, 85]. BNP and its prohormone (NT-proBNP) are secreted by the heart atria secondary to stretching of cardiac myocytes or direct cell damage. The degree of rise of these hormones correlates directly to the severity of cirrhosis and cardiac dysfunction [86, 87]. It is recommended that patients with NT-proBNP levels >290 pg/mL should undergo further cardiac evaluation [88].

**Table 9.4** Differentiation between acute ischemic hepatitis and cardiac cirrhosis

	Acute ischemic hepatitis	Cardiac cirrhosis
Etiology	Acute heart failure (left)	Chronic heart failure (right)
Pathophysiology	Hypoxia	Perisinusoidal edema
	Zone 3 necrosis	Increased lymphatic drainage
		Zone 3: alternating necrosis and hemorrhage
		Sinusoidal thrombosis
Clinical presentation	Non-specific (nausea, vomiting, jaundice)	Edema, ascites, jaundice
Clinical biomarkers		
Bilirubin	↑↑↑	↑
ALT and AST	↑↑↑	Normal/↑
LDH	↑↑↑	Normal/↑
Prothrombin time	Normal or prolonged	Prolonged
ALP	Increased	Normal or mild elevation
Albumin	Normal	↓↓
Treatment	Oxygen therapy Inotropic agents Vasopressors Diuretics	ACE Inhibitors B-blockers Diuretics
Prognosis	Self-limiting	Gradual progressive decline

Troponins are specific markers of cardiac insult and are encoded by three distinct gene products: troponin C, cardiac troponin I and T (cTnT). Troponin I levels are increased in patients with alcoholic cirrhosis, and the concentration level is associated with low stroke volume and LV mass. However, the degree of rise in troponin I level is not associated with severity of cirrhosis or portal HTN [89]. The level of cTnT, on the other hand, has been shown to correlate directly with disease severity and mortality in cirrhosis [90].

### 9.3.3 Cardiac Imaging in Liver Disease

Echocardiography is an ultrasound based imaging modality that provides assessment of cardiac structure, function, and hemodynamics. Echocardiography provides a noninvasive characterization of left ventricular and right ventricular systolic performance as well as cardiac volumes and cardiac valves. Doppler echocardiography can also be used to estimate right ventricular pressures. Furthermore, using tricuspid velocity jet to measure right ventricular systolic pressures, pulmonary artery systolic pressures can be calculated via adding estimated right atrial pressures [62].

Doppler echocardiography can also be used to assess left ventricular diastolic function. Placing a sample of volume at the tip of mitral valve and using pulse-wave Doppler, velocities of LV inflow during early, rapid passive filling (E wave), and during atrial contraction (A wave) can be measured. E-wave velocity depicts the left atrium-left ventricle pressure gradient during early diastole. This gradient is affected by changes in the rate of LV relaxation and left atrial pressure. A-wave velocity depicts the left atrium-left ventricle pressure gradient during late diastole, and is affected by LV compliance and LA contractile function. This allows for measurement of E/A ratio, with ratios <1 suggesting diastolic dysfunction. The E wave deceleration time (time measured from the maximum E point to baseline, normally <220 ms) and isovolumic relaxation time (time interval between aortic valve closure and mitral valve opening) also may reflect diastolic dysfunction. Diastolic dysfunction is characterized by a decreased E/A ratio with prolonged deceleration and isovolumetric relaxation times. An enlarged left atrium also reflects chronic diastolic dysfunction. Normally, Doppler velocities are dependent on filling pressures at the time of measurement, whereas LA volume reflects the cumulative effect of filling pressures over time [91, 92].

Cardiac magnetic resonance (CMR) imaging is the gold standard for measurement of LV function [93]. Contrast-enhanced CMR has the added benefit of demonstrating subclinical myocardial changes prior to the onset of occult LV dysfunction [94]. Abnormalities in T2-weighted images have been described in acute myocardial injury and inflammation. T1-weighted images are a newer technique, which can elucidate the presence of diffuse myocardial fibrosis or infiltrative disease as measured by T1 relaxation times [95]. Diffuse myocardial fibrosis has been shown to be closely related to diastolic dysfunction. Currently, few studies have applied CMR in cirrhosis. (1) In an animal model, CMR has been used to show hyperdynamic LV function and increased LV thickness [96]. (2) CMR was used to demonstrate elevated pulmonary wedge pressure and atrial enlargement within the first 24 h after TIPS in 11 cirrhotic patients [97]. (3) Increased cardiac volumes and diastolic dysfunction was seen in 19 patients with mild cirrhosis after dobutamine-induced stress CMR [98]. (4) Use of contrast-enhanced CMR in cirrhotic cardiomyopathy patients detected myocardial changes in awaiting liver transplant, similar to those myocardial changes found in myocarditis [99].

Cardiac stress testing is an important tool to risk stratify cirrhotic patients awaiting transplantation or other invasive therapies. Cardiac stress testing can be performed either via exercise or pharmacologic therapy. Ideally, the test of choice is exercise based because it provides important prognostic information. For those patients

unable to exercise, dobutamine is the pharmacologic agent of choice. Dobutamine is a synthetic drug with  $\beta_1$  (increase cardiac contractility and cardiac output), and  $\beta_2$  properties (arterial vasodilator). The discrepancy of blood flow to normal myocardium and areas of disease can be assessed via myocardial perfusion imaging utilizing echocardiography, cardiac magnetic resonance imaging (CMR), or single-photon emission computed tomography (SPECT) [100]. Although dobutamine stress echo is widely used for cardiovascular risk assessment prior to liver transplant [12, 101], its positive predictive value in detecting CAD in cirrhotic patients is debated. Due to the concomitant use of beta blockers or chronotropic incompetence, in 25–56% of patients dobutamine stress echocardiograms are inconclusive because of failure to reach the target heart rate (85% predicted maximum heart rate) [102]. Pharmacologic vasodilator stress testing induces coronary vasodilation and increased myocardial blood flow to meet the metabolic demands of the body. Coronary beds containing significant disease fail to dilate and increase blood flow, and regional differences in blood flow can be seen using SPECT nuclear imaging. In addition, in patients who have undergone prior revascularization, SPECT is the modality of choice [103].

Surgical outcomes of liver transplant are dependent on both the severity of the liver disease and the underlying comorbidities. In the post-transplant period, cardiovascular complications are the leading cause of non-graft related deaths [104]. Cardiac evaluation prior to liver transplantation should include an electrocardiogram and echocardiogram. CAD screening, with stress testing or coronary angiography should be performed routinely because patients with cirrhosis are possibly at higher risk of CAD than the general population. In liver transplant candidates 13% of the patients were found to have moderate to severe CAD without clinical symptoms [105]. Right heart catheterization may be warranted if echocardiography suggests pulmonary hypertension. In patients with moderate to severe pulmonary hypertension, liver transplant is contraindicated due to significant increased transplantation-related mortality [106].

### 9.3.4 Intensive Care Unit Evaluation

Patients with liver disease over time progress to worsening liver function with occurrence of portal hypertension and hepatic failure leading to end-stage liver disease and eventually to death. Acute decompensation is often unpredictable and may require monitoring in the ICU. Most frequently patients are admitted to the ICU for variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis, jaundice, and sepsis [107]. The estimated annual incidence of admission to the ICU related to cirrhosis in the United States

is roughly 26,000, with an estimated cost of US \$3 billion [108]. Cirrhotic patients admitted to the hospital and/or the ICU have a mortality ranging from 34 to 85% [109]. Prognostic scoring systems, such as Sequential Organ Failure Assessment (SOFA), and the Acute Physiology And Chronic Health Evaluation (APACHE) on admission and within 24 h to the ICU have been used and validated to predict outcomes [110]. Child-Pugh the Model for End-Stage Liver Disease have been the most widely used hepatic specific scores for predicting mortality in patients awaiting liver transplantation. Patients with known cirrhosis, and an acute decompensation leading to organ failure are classified as having acute on chronic liver failure (ACLF) [111].

The diagnosis of ACLF is made using the Chronic Liver Failure Organ Failure (CLIF) score, and prognosis is dependent on organ failure (see Table 9.5). ACLF is present in approximately 30% of hospitalized cirrhotic patients who present with either an identifiable source, such as viral infection or drug exposure, or an unidentifiable source. The presence of ACLF confers a 28-day mortality rate 15 times higher than in those cirrhotic patients without ACLF [111, 112]. Recently, a Consensus meeting regarding management of critically ill cirrhotic patients endorsed by the American Society of Transplantation, American Society of Transplant Surgeons, and the European Association for the Study of Liver disease outlined a multi-disciplinary approach to optimize ICU management of these patients [113].

Initial evaluation of an acutely decompensated cirrhotic patient revolves around hemodynamic assessment. Due the underlying cardiac dysfunction multiple organs are at risk,

and prompt recognition and treatment of the underlying hemodynamic challenges can reverse or halt the progression of the disease. The pathophysiology of circulatory dysfunction in ACLF is similar to acute liver failure, and relates to arterial vasodilatation leading to impaired tissue perfusion. Extensive splanchnic vasodilatation results in effective hypovolemia, activation of RAAS, and retention of water and sodium. RAAS activation results in worsening renal function secondary to vasoconstriction and abdominal compartment syndrome in patients with tense ascites [114]. Hemodynamic collapse leads to further hepatocyte injury and inflammation, resulting in worsening cirrhosis, and contributes significantly to prognosis [115, 116].

Resuscitative efforts are similar to those seen in septic shock. Goals of therapy are to ensure adequate organ perfusion, with a target mean arterial pressure around  $\geq 60$  mmHg [117]. No specific value for ventricular filling pressures, lactate, or  $S_{cv}O_2$  is recommended [118]. On the contrary, data suggest that excessive fluid administration can have deleterious effects due to increasing tissue edema and increasing total body volume. As a result, patients develop extracellular and pulmonary edema, and ascites. Ascites can lead to increased intra-abdominal pressures resulting in further pulmonary, cardiac, renal, and hepatic dysfunction [119–121]. In patients who present with tense ascites and clinical suspicion for abdominal hypertension, therapeutic paracentesis is recommended [122].

In patients with circulatory shock hemodynamic monitoring may be useful to more fully characterize hemodynamics even though distributive shock is most commonly observed (Table 9.6). The placement of arterial catheters is recommended to guide ongoing resuscitative efforts to prevent volume overload [118]. Due to its dynamic format, echocardiography is recommended as first line option for initial evaluation of circulatory failure [123]. Serial central venous pressure measurements during active volume resuscitation provide a better assessment than a single measurement [124]. However, CVP may be elevated secondary to increased intra-abdominal pressures and CVP may increase without an improvement in cardiac preload. Patients with clinical suspicion for right ventricular dysfunction or pulmonary hypertension should be considered for monitoring using a pulmonary artery (PA) catheter. PA catheters are especially useful during undifferentiated shock and assessment of high

**Table 9.5** Organ failure and mortality in acute on chronic liver failure

ACLF grade	Characteristics	Mortality at 28 days (%)	Mortality at 90 days (%)
ALD alone	No organ failure	4.7	14
Grade 1	One organ failure	22.1	40.7
Grade 2	Two organ failure	32	52.3
Grade 3	Three organ failure	76.7	79.1

Organ failure was defined as liver failure, hepatic encephalopathy, kidney failure, circulatory failure, or respiratory failure. Data from Moreau, R., et al., Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*, 2013; **144**:1426–37, 1437.e1–9

**Table 9.6** Hemodynamic variables in various types of shock

	Hypovolemic	Cardiogenic	Distributive	Obstructive
Pulmonary capillary wedge pressure	Normal or decreased late	High	Normal or decreased late	Normal or decreased late
Cardiac output	Normal or decreased late	Low	High	Normal or decreased late
Systemic vascular resistance	High	High	Low	High
Mixed venous oxyhemoglobin saturation	>65% or <65% late	<65%	>65%	>65%

pressure versus low pressure pulmonary edema and pulmonary infections [113].

In patients with distributive shock, crystalloids are the initial fluid of choice at an initial dose of 10–20 ml/kg [125]. In patients who develop signs of volume overload with impaired oxygenation, or in whom edema and ascites worsen dramatically, fluid administration should be discontinued. CVP can be used as a measure fluid status (stopping fluids when CVP > 12 mmHg) but dynamic measures including respiratory variation of pulse pressure, vena cava diameter, or stroke volume variation, are much more reliable indices of whether fluid infusion will increase stroke volume and thus cardiac output and blood pressure.

Use of albumin in patients with cirrhosis is based on its theoretical biological properties [126]. Albumin plus antibiotics has been shown to be superior to antibiotics alone in patients with SBP, and in the prevention of type-1 hepatorenal syndrome [127]. Albumin has also been recommended to prevent cardiac dysfunction after large volume (>5 L) paracentesis [128, 129]. Trials have shown improvement in renal function after administration of albumin in cirrhotic patients with infections other than SBP [130, 131], but clinical trial data showing improvement in hard outcomes with albumin use in patients with liver failure are lacking.

Shock refractory to volume resuscitation should be treated with vasopressors. The initial vasopressor of choice is norepinephrine, which has fewer side effects than dopamine or epinephrine [132]. Vasopressin or terlipressin are second line agents of choice in patient with persistent hypotension despite use of norepinephrine, or hypotension resistant to norepinephrine [133, 134].

Cirrhotic patients who are critically ill are at an increased risk of adrenal insufficiency. Currently there is no consensus for the diagnosis of adrenal insufficiency in patient with cirrhosis, because adrenal inefficiency could result from underlying liver disease rather than from critical illness [135, 136]. Studies have shown that use of corticosteroids results in reduction in vasopressor requirement and increased rates of shock reversal [137, 138]. However, survival benefit was only shown in some [44, 139], and not all studies [137, 138]. In patients that require increasing levels of vasopressors, hydrocortisone 200–300 mg/day in divided doses should be considered, and stopped following improvement in hemodynamics [136, 140].

### 9.3.5 Transjugular Intrahepatic Portosystemic Shunts

*Portal hypertension* (PH) is one of the most common causes of complications such as variceal bleeding, ascites, and death in patients with cirrhosis [32, 141, 142]. PH develops as an effect of increasing resistance to portal blood flow. It is

defined as an increase of pressure gradient of 5 mmHg above the upper normal limit in the pressure gradient between the portal vein and the inferior vena cava (portal pressure gradient). PH becomes clinically significant when the portal pressure gradient exceeds 10 mmHg, whereas the normal pressure gradient is <5 mmHg [143, 144]. As PH worsens, portal-systemic collaterals develop and divert portal blood flow to systemic circulation. Therefore, the primary interventions to reducing PH complications are aimed at reducing the portal pressure gradient, either pharmacologically or through intervention [145].

*Transjugular Intrahepatic Portosystemic Shunts* (TIPS) is a percutaneously created system between the portal vein and the hepatic vein. The primary purpose of this procedure is to create a low-resistance channel between the intrahepatic portion of the portal vein and the hepatic vein from a transjugular approach [145, 146]. The Society of Interventional Radiology guidelines classify successful outcome to include the creation of a shunt and decrease in portal pressure gradient to <12 mmHg [147, 148]. In most reported series, the cited success rate of TIPS to alleviate portal vein pressure is >90% [149–151]. Procedure-related mortality is low, approximately 1.2% [152]. Long-term outcome is dependent on the condition of the patient and the underlying indication for TIPS [153].

TIPS results in significant hemodynamic changes due to increased preload and circulatory volume. As the high volume splanchnic blood flow enters systemic circulation, central and pulmonary capillary wedge pressures rise twofold [97, 154]. As a result, studies have reported increased cardiac output for up to 1 year post procedure [155], and cases of overt heart failure [156]. In patients with diastolic dysfunction at baseline there is reported lower post-TIPS ascites clearance, and decreased probability of survival at 1 year than those without [157]. The inability of the non-compliant left ventricle to handle the increase in volume further decreases cardiac output and central blood volume. Vasoactive substances, having bypassed the hepatic metabolism, reach systemic circulation and can cause further hemodynamic decompensation [158]. These clinically significant complications require careful evaluation of patients proceeding to TIPS.

Guidelines recommend evaluation of patients with history of CHF, tricuspid regurgitation, cardiomyopathy, or pulmonary HTN prior to TIPS [159]. Based on clinical picture and risk factors, evaluation may include echocardiogram, cardiology consultation, and possibly a trial of fluid challenge. The guidelines do not recommend routine echocardiography in the absence of a cardiac history [159]. However, since up to 16% of patients referred for liver transplantation may have pulmonary HTN, other experts feel that all patients should undergo an echocardiogram, a rapid and noninvasive test, prior to TIPS [160]. In general, a history of congestive heart failure and severe pulmonary



HTN (mean pulmonary pressures >45 mmHg) are absolute contraindications to TIPS [160].

### 9.3.6 Liver Transplantation

Liver transplantation has profound effects on the heart. The main goal before transplantation is to monitor cardiac function to prevent development of post-operative heart failure. In the immediate post-operative period there are significant changes in preload and afterload due to intraoperative fluid administration and clamping of the hepatic vein [161]. Patients with cirrhotic cardiomyopathy may be unable to tolerate the excessive volume, thus unmasking the underlying myocardial dysfunction. On the other hand, clamping of the major vessels results in reduced ventricular preload and cardiac output.

Post-transplant reperfusion has been associated with acidosis, hyperkalemia, hypothermia, and other metabolic abnormalities causing a decrease in cardiac function [12, 162]. Restoration of normal portal pressures and liver function, along with hypertensive effects of the immunosuppressive medications, can precipitate an acute increase in systemic vascular resistance. This in turn leads to an increase in arterial hypertension and cardiac afterload, which can precipitate acute left ventricular failure and pulmonary edema. Other heart-related complications include reperfusion syndrome, arrhythmias, sudden cardiac death, and myocardial infarction [163–165].

The goal of pre-transplant cardiac evaluation is to assess perioperative risk and to identify concomitant cardiopulmonary disorders which would be prohibitive of liver transplant. Even though the prevalence of systemic hypertension is low secondary to systemic vasodilation, and lipids are generally low due to abnormal hepatic synthetic function, coronary artery disease is at least as frequent in liver transplant patients as in the general population [166]. Guidelines by the American Association for the Study of Liver Diseases and the American Society of Transplantation recommend that all pre-transplant patients undergo noninvasive testing with echocardiography [167]. Patients with advanced liver disease may fail to reach the target heart rate required during a standard exercise test. These patients should undergo pharmacologic stress test with adenosine, dipyridamole, or dobutamine, to screen for coronary disease. Most often dobutamine stress echocardiography is the initial imaging modality of choice.

Cardiac catheterization is recommended for patients with positive stress tests. Careful consideration has to be given to patients with advanced liver disease due to increased vascular complications as a result of underlying coagulopathy [168]. Additionally, patients with cirrhosis are at an increased of contrast-induced nephropathy because of baseline renal dysfunction. Cardiac revascularization should be considered

in patients with significant coronary artery stenosis (>70%). It has become commonplace to revascularize patients prior to liver transplant [167]. Bare metal stents are favored over drug-eluting stents due to the shorter duration of requisite dual antiplatelet therapy (clopidogrel and aspirin) [169]. Recent studies have shown superior outcomes in patients who have undergone cardiac stenting with single vessel disease as compared to patients with prior coronary artery bypass graft for multivessel disease [169].

Pulmonary HTN, defined as mean pulmonary artery pressure  $\geq 25$  mmHg, occurring in the presence of portal HTN is referred to as portopulmonary HTN [170]. The presence of pulmonary HTN does not correlate with the severity or the etiology of portal HTN. Portopulmonary HTN is present in 4–8% of liver transplant candidates [171]. Mean pulmonary artery pressure (MPAP) is directly correlative of outcomes. In a registry from Mayo Clinic mortality was reported as 50% with MPAP >35 mmHg and 100% with MPAP >100 mmHg [172]. Contrast enhanced echocardiography is the initial screening test to estimate right ventricular systolic pressure. Right heart catheterization is the gold standard confirmatory test and should be performed in all patients with MPAP of >35 mmHg via echocardiography. In addition, right heart catheterization is useful to measure elevated pulmonary vascular resistance ( $\geq 240$ -dynes.s/cm) and pulmonary capillary wedge pressure  $\leq 15$  mmHg. During right heart catheterization with vasodilator therapy if MPAP can be reduced to <35 mmHg, and pulmonary vascular resistance can be reduced to <400 dynes.s/cm, liver transplant is possible [173]. Portopulmonary HTN can improve with liver transplant and vasodilator therapy can ultimately be discontinued in subset of patients [174, 175]. Clinically significant improvement in cardiac wall thickness, systolic function, diastolic function, and exercise capacity during stress was observed after 6 months from liver transplant [176]. The current opinion is that cardiac dysfunction may last from a minimum of few days to a period of 6 months [177].

### Conclusion

Liver failure is a complex disease process that effects almost every organ of the body. Management of this disease entity requires multispecialty approach. Acute care for patients suffering from liver failure usually takes place in the ICU. Despite the extraordinary level of care provided in the ICU, mortality remains high. Acute on chronic liver failure is acute decompensation and associated with poor short term prognosis. The degree of cardiac derangement correlates with the degree of liver dysfunction, and may lead to other disease processes such as hepato-renal syndrome and hepatic encephalopathy. Prompt recognition and treatment of the underlying cause of acute decompensation is the only definitive therapy for this devastating disease process.



## References

- Rychik J, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol*. 2012;33(7):1001–12.
- Fang JC, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. *J Card Fail*. 2015;21(6):519–34.
- Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest*. 1953;32(10):1025–33.
- Waseem N, Chen PH. Hypoxic hepatitis: a review and clinical update. *J Clin Transl Hepatol*. 2016;4(3):263–8.
- Ford RM, Book W, Spivey JR. Liver disease related to the heart. *Transplant Rev (Orlando)*. 2015;29(1):33–7.
- Chayanupatkul M, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. *Hepatol Int*. 2014;8(3):308–15.
- Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Gut*. 2008;57(2):268–78.
- Levy D, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397–402.
- Lunseith JH, Olmstead EG, Abboud F. A study of heart disease in one hundred eight hospitalized patients dying with portal cirrhosis. *AMA Arch Intern Med*. 1958;102(3):405–13.
- Pozzi M, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology*. 1997;26(5):1131–7.
- Zardi EM, et al. Cirrhotic cardiomyopathy. *J Am Coll Cardiol*. 2010;56(7):539–49.
- Myers RP, Lee SS. Cirrhotic cardiomyopathy and liver transplantation. *Liver Transpl*. 2000;6(4 Suppl 1):S44–52.
- Pendyal A, Gelow JM. Cardiohepatic interactions: implications for management in advanced heart failure. *Heart Fail Clin*. 2016;12(3):349–61.
- Ishibashi H, et al. Liver architecture, cell function, and disease. *Semin Immunopathol*. 2009;31(3):399–409.
- Rappaport AM, et al. Subdivision of hexagonal liver lobules into a structural and functional unit; role in hepatic physiology and pathology. *Anat Rec*. 1954;119(1):11–33.
- Henrion J, et al. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore, Md)*. 2003;82(6):392–406.
- Seeto RK, Fenn B, Rockey DC. Ischemic hepatitis: clinical presentation and pathogenesis. *Am J Med*. 2000;109(2):109–13.
- Fuhrmann V, et al. Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. *Intensive Care Med*. 2009;35(8):1397–405.
- Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. *Int J Angiol*. 2011;20(3):135–42.
- Gitlin N, Serio KM. Ischemic hepatitis: widening horizons. *Am J Gastroenterol*. 1992;87(7):831–6.
- Cassidy WM, Reynolds TB. Serum lactic dehydrogenase in the differential diagnosis of acute hepatocellular injury. *J Clin Gastroenterol*. 1994;19(2):118–21.
- Sola E, Gines P. Renal and circulatory dysfunction in cirrhosis: current management and future perspectives. *J Hepatol*. 2010;53(6):1135–45.
- Moller S, Krag A, Bendtsen F. Kidney injury in cirrhosis: pathophysiological and therapeutic aspects of hepatorenal syndromes. *Liver Int*. 2014;34(8):1153–63.
- Fede G, et al. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol*. 2015;28(1):31–40.
- Whittle BJ, Moncada S. Nitric oxide: the elusive mediator of the hyperdynamic circulation of cirrhosis? *Hepatology*. 1992;16(4):1089–92.
- Battista S, et al. Hyperdynamic circulation in patients with cirrhosis: direct measurement of nitric oxide levels in hepatic and portal veins. *J Hepatol*. 1997;26(1):75–80.
- Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21(1):125–40.
- Lee FY, et al. The role of nitric oxide in the vascular hyporesponsiveness to methoxamine in portal hypertensive rats. *Hepatology*. 1992;16(4):1043–8.
- Moller S, et al. Determinants of the hyperdynamic circulation and central hypovolaemia in cirrhosis. *Gut*. 2011;60(9):1254–9.
- Niederberger M, et al. Normalization of nitric oxide production corrects arterial vasodilation and hyperdynamic circulation in cirrhotic rats. *Gastroenterology*. 1995;109(5):1624–30.
- Prin M, Bakker J, Wagener G. Hepatosplanchnic circulation in cirrhosis and sepsis. *World J Gastroenterol*. 2015;21(9):2582–92.
- Garcia-Tsao G, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007;46(3):922–38.
- Donnelly MC, Hayes PC, Simpson KJ. Role of inflammation and infection in the pathogenesis of human acute liver failure: clinical implications for monitoring and therapy. *World J Gastroenterol*. 2016;22(26):5958–70.
- O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342(8866):273–5.
- Ostapowicz G, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137(12):947–54.
- Bernal W, et al. Acute liver failure. *Lancet*. 2010;376(9736):190–201.
- Acharya SK, et al. Etiopathogenesis of acute hepatic failure: Eastern versus Western countries. *J Gastroenterol Hepatol*. 2002;17(Suppl 3):S268–73.
- Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2012;55(3):965–7.
- Lee WM. Acute liver failure. *N Engl J Med*. 1993;329(25):1862–72.
- Shakil AO, et al. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. *Dig Dis Sci*. 2000;45(2):334–9.
- Chavarria L, et al. Neuroimaging in acute liver failure. *Neurochem Int*. 2011;59(8):1175–80.
- Munoz SJ. Difficult management problems in fulminant hepatic failure. *Semin Liver Dis*. 1993;13(4):395–413.
- Bihari D, et al. Tissue hypoxia during fulminant hepatic failure. *Crit Care Med*. 1985;13(12):1034–9.
- Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology*. 2002;36(2):395–402.
- Lee WM, et al. Acute liver failure: summary of a workshop. *Hepatology*. 2008;47(4):1401–15.
- Fouad YM, Yehia R. Hepato-cardiac disorders. *World J Hepatol*. 2014;6(1):41–54.
- Jiao J, Friedman SL, Aloman C. Hepatic fibrosis. *Curr Opin Gastroenterol*. 2009;25(3):223–9.
- Wong RJ, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148(3):547–55.
- Murray CJ, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310(6):591–608.
- Poelzl G, Auer J. Cardiohepatic syndrome. *Curr Heart Fail Rep*. 2015;12(1):68–78.
- Sucharov CC. Beta-adrenergic pathways in human heart failure. *Expert Rev Cardiovasc Ther*. 2007;5(1):119–24.
- Ma Z, Miyamoto A, Lee SS. Role of altered beta-adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. *Gastroenterology*. 1996;110(4):1191–8.

53. Liu H, Ma Z, Lee SS. Contribution of nitric oxide to the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. *Gastroenterology*. 2000;118(5):937–44.
54. Pacher P, Batkai S, Kunos G. Cirrhotic cardiomyopathy: an endocannabinoid connection? *Br J Pharmacol*. 2005;146(3):313–4.
55. Iwaisako K, Brenner DA, Kisseleva T. What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. *J Gastroenterol Hepatol*. 2012;27(Suppl 2):65–8.
56. Singal AG, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol*. 2010;8(3):280–8. 288.e1.
57. Alvarez MA, et al. Long-term clinical course of decompensated alcoholic cirrhosis: a prospective study of 165 patients. *J Clin Gastroenterol*. 2011;45(10):906–11.
58. Niemela O, et al. Markers of fibrogenesis and basement membrane formation in alcoholic liver disease. Relation to severity, presence of hepatitis, and alcohol intake. *Gastroenterology*. 1990;98(6):1612–9.
59. Reynolds TB, et al. Spontaneous decrease in portal pressure with clinical improvement in cirrhosis. *N Engl J Med*. 1960;263:734–9.
60. Runyon BA. Historical aspects of treatment of patients with cirrhosis and ascites. *Semin Liver Dis*. 1997;17(3):163–73.
61. Regan TJ, et al. Ventricular function in noncardiacs with alcoholic fatty liver: role of ethanol in the production of cardiomyopathy. *J Clin Invest*. 1969;48(2):397–407.
62. Rudski LG, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685–713. quiz 786–8.
63. Krag A, et al. The cardiorenal link in advanced cirrhosis. *Med Hypotheses*. 2012;79(1):53–5.
64. Yang YY, Lin HC. The heart: pathophysiology and clinical implications of cirrhotic cardiomyopathy. *J Chin Med Assoc*. 2012;75(12):619–23.
65. Moller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J*. 2013;34(36):2804–11.
66. Karagiannakis DS, et al. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. *Hepatol Int*. 2014;8(4):588–94.
67. Ahmed SS, et al. Cardiac function in alcoholics with cirrhosis: absence of overt cardiomyopathy—myth or fact? *J Am Coll Cardiol*. 1984;3(3):696–702.
68. Ingles AC, et al. Limited cardiac preload reserve in conscious cirrhotic rats. *Am J Physiol*. 1991;260(6 Pt 2):H1912–7.
69. Bernardi M, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27(1):28–34.
70. Ward CA, et al. Potassium currents in atrial and ventricular myocytes from a rat model of cirrhosis. *Am J Physiol*. 1997;273(2 Pt 1):G537–44.
71. Ward CA, Liu H, Lee SS. Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy. *Gastroenterology*. 2001;121(5):1209–18.
72. Henriksen JH, et al. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. *J Hepatol*. 2004;40(2):239–46.
73. Giannelli V, et al. Beta-blockers in liver cirrhosis. *Ann Gastroenterol*. 2014;27(1):20–6.
74. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int*. 2003;23(4):243–8.
75. Trevisani F, et al. QT interval prolongation by acute gastrointestinal bleeding in patients with cirrhosis. *Liver Int*. 2012;32(10):1510–5.
76. Zambruni A, et al. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. *J Hepatol*. 2008;48(3):415–21.
77. Ruiz-del-Arbol L, et al. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology*. 1997;113(2):579–86.
78. Ruiz-del-Arbol L, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology*. 2003;38(5):1210–8.
79. Ruiz-del-Arbol L, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology*. 2005;42(2):439–47.
80. Runyon BA. A primer on detecting cirrhosis and caring for these patients without causing harm. *Int J Hepatol*. 2011;2011:801983.
81. Valeriano V, et al. Modification of cardiac function in cirrhotic patients with and without ascites. *Am J Gastroenterol*. 2000;95(11):3200–5.
82. Nagueh SF, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10(2):165–93.
83. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *Br Heart J*. 1951;13(3):273–93.
84. Gines P, et al. Atrial natriuretic factor in cirrhosis with ascites: plasma levels, cardiac release and splanchnic extraction. *Hepatology*. 1988;8(3):636–42.
85. Salerno F, et al. Atrial natriuretic factor in cirrhotic patients with tense ascites. Effect of large-volume paracentesis. *Gastroenterology*. 1990;98(4):1063–70.
86. Wong F, et al. Brain natriuretic peptide: is it a predictor of cardiomyopathy in cirrhosis? *Clin Sci (Lond)*. 2001;101(6):621–8.
87. Henriksen JH, et al. Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. *Gut*. 2003;52(10):1511–7.
88. Raedle-Hurst TM, et al. Validity of N-terminal propeptide of the brain natriuretic peptide in predicting left ventricular diastolic dysfunction diagnosed by tissue Doppler imaging in patients with chronic liver disease. *Eur J Gastroenterol Hepatol*. 2008;20(9):865–73.
89. Pateron D, et al. Elevated circulating cardiac troponin I in patients with cirrhosis. *Hepatology*. 1999;29(3):640–3.
90. Wiese S, et al. Cardiac and proinflammatory markers predict prognosis in cirrhosis. *Liver Int*. 2014;34(6):e19–30.
91. Nagueh SF, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277–314.
92. Wiese S, Hove JD, Moller S. Cardiac imaging in patients with chronic liver disease. *Clin Physiol Funct Imaging*. 2017;37:347.
93. Lima JA, Desai MY. Cardiovascular magnetic resonance imaging: current and emerging applications. *J Am Coll Cardiol*. 2004;44(6):1164–71.
94. Lawton JS, et al. Magnetic resonance imaging detects significant sex differences in human myocardial strain. *Biomed Eng Online*. 2011;10:76.
95. Iles L, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol*. 2008;52(19):1574–80.
96. Desai MS, et al. Hypertrophic cardiomyopathy and dysregulation of cardiac energetics in a mouse model of biliary fibrosis. *Hepatology*. 2010;51(6):2097–107.
97. Kovacs A, et al. Short-term effects of transjugular intrahepatic shunt on cardiac function assessed by cardiac MRI: preliminary results. *Cardiovasc Intervent Radiol*. 2010;33(2):290–6.
98. Krag A, et al. Cardiac function in patients with early cirrhosis during maximal beta-adrenergic drive: a dobutamine stress study. *PLoS One*. 2014;9(10):e109179.

99. Lossnitzer D, et al. Myocardial late gadolinium enhancement cardiovascular magnetic resonance in patients with cirrhosis. *J Cardiovasc Magn Reson*. 2010;12:47.
100. Salerno M, Beller GA. Noninvasive assessment of myocardial perfusion. *Circ Cardiovasc Imaging*. 2009;2(5):412–24.
101. Rudzinski W, et al. New index for assessing the chronotropic response in patients with end-stage liver disease who are undergoing dobutamine stress echocardiography. *Liver Transpl*. 2012;18(3):355–60.
102. Ripoll C, et al. The heart in liver transplantation. *J Hepatol*. 2011;54(4):810–22.
103. Underwood SR, et al. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging*. 2004;31(2):261–91.
104. Eimer MJ, et al. Frequency and significance of acute heart failure following liver transplantation. *Am J Cardiol*. 2008;101(2):242–4.
105. Carey WD, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation*. 1995;59(6):859–64.
106. Murray KF, Carithers RL Jr, AASLD. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology*. 2005;41(6):1407–32.
107. Saliba F, et al. Cirrhotic patients in the ICU: prognostic markers and outcome. *Curr Opin Crit Care*. 2013;19(2):154–60.
108. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care*. 2011;17(2):165–9.
109. Cholongitas E, et al. Review article: scoring systems for assessing prognosis in critically ill adult cirrhotics. *Aliment Pharmacol Ther*. 2006;24(3):453–64.
110. Thabut D, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology*. 2007;46(6):1872–82.
111. Jalan R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60(6):1310–24.
112. Jalan R, et al. Acute-on chronic liver failure. *J Hepatol*. 2012;57(6):1336–48.
113. Nadim MK, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepatol*. 2016;64(3):717–35.
114. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361(13):1279–90.
115. Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7):1426–37. 1437.e1–9.
116. Jalan R, et al. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol*. 2015;62(4):831–40.
117. LeDoux D, et al. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med*. 2000;28(8):2729–32.
118. Cecconi M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795–815.
119. Rhodes A, et al. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med*. 2002;28(3):256–64.
120. Rosenberg AL, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med*. 2009;24(1):35–46.
121. National Heart L, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564–75.
122. Aspesi M, et al. The abdominal compartment syndrome. Clinical relevance. *Minerva Anesthesiol*. 2002;68(4):138–46.
123. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J*. 2003;146(3):388–97.
124. Monnet X, Teboul JL. Assessment of volume responsiveness during mechanical ventilation: recent advances. *Crit Care*. 2013;17(2):217.
125. Finfer S, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247–56.
126. Arroyo V, Garcia-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol*. 2014;61(2):396–407.
127. Sort P, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341(6):403–9.
128. Sola-Vera J, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology*. 2003;37(5):1147–53.
129. Moreau R, et al. Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot trial. *Liver Int*. 2006;26(1):46–54.
130. Guevara M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol*. 2012;57(4):759–65.
131. Thevenot T, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol*. 2015;62(4):822–30.
132. De Backer D, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–89.
133. O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. *Lancet*. 2002;359(9313):1209–10.
134. Delmas A, et al. Clinical review: vasopressin and terlipressin in septic shock patients. *Crit Care*. 2005;9(2):212–22.
135. Fede G, et al. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology*. 2012;55(4):1282–91.
136. Tsai MH, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology*. 2006;43(4):673–81.
137. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int*. 2003;23(2):71–7.
138. Arabi YM, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ*. 2010;182(18):1971–7.
139. Fernandez J, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44(5):1288–95.
140. Annane D, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862–71.
141. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med*. 2010;362(9):823–32.
142. Bosch J, et al. The management of portal hypertension: rational basis, available treatments and future options. *J Hepatol*. 2008;48(Suppl 1):S68–92.
143. Sanyal AJ, et al. Portal hypertension and its complications. *Gastroenterology*. 2008;134(6):1715–28.
144. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis*. 2001;5(3):645–63.
145. Siramolpiwat S. Transjugular intrahepatic portosystemic shunts and portal hypertension-related complications. *World J Gastroenterol*. 2014;20(45):16996–7010.
146. Rosch J, Hanafee WN, Snow H. Transjugular portal venography and radiologic portacaval shunt: an experimental study. *Radiology*. 1969;92(5):1112–4.
147. Haskal ZJ, et al. Quality improvement guidelines for transjugular intrahepatic portosystemic shunts. SCVIR Standards of Practice Committee. *J Vasc Interv Radiol*. 2001;12(2):131–6.
148. Haskal ZJ, et al. Quality improvement guidelines for transjugular intrahepatic portosystemic shunts. *J Vasc Interv Radiol*. 2003;14(9 Pt 2):S265–70.



149. Krajina A, et al. Transjugular intrahepatic portosystemic shunt (TIPS) in the treatment of symptomatic portal hypertension. *Cas Lek Cesk*. 1996;135(18):584–8.
150. Cabrera J, et al. Transjugular intrahepatic portosystemic shunt versus sclerotherapy in the elective treatment of variceal hemorrhage. *Gastroenterology*. 1996;110(3):832–9.
151. Hayek G, et al. Long-term outcome and analysis of dysfunction of transjugular intrahepatic portosystemic shunt placement in chronic primary budd-chiari syndrome. *Radiology*. 2017; 283:280.
152. Tripathi D, et al. Ten years' follow-up of 472 patients following transjugular intrahepatic portosystemic stent-shunt insertion at a single centre. *Eur J Gastroenterol Hepatol*. 2004;16(1):9–18.
153. Jalan R, et al. Prospective evaluation of haematological alterations following the transjugular intrahepatic portosystemic stent-shunt (TIPSS). *Eur J Gastroenterol Hepatol*. 1996;8(4):381–5.
154. Huonker M, et al. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. *Gut*. 1999;44(5):743–8.
155. Moller S, et al. New insights into cirrhotic cardiomyopathy. *Int J Cardiol*. 2013;167(4):1101–8.
156. Braverman AC, et al. High-output congestive heart failure following transjugular intrahepatic portal-systemic shunting. *Chest*. 1995;107(5):1467–9.
157. Cazzaniga M, et al. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. *Gut*. 2007;56(6):869–75.
158. Trevisani F, et al. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. *J Hepatol*. 2003;38(4): 461–7.
159. Boyer TD, Haskal ZJ, D. American Association for the Study of Liver. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. *Hepatology*. 2010;51(1):306.
160. Hooper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet*. 2004;363(9419): 1461–8.
161. Aggarwal S, et al. Postreperfusion syndrome: hypotension after reperfusion of the transplanted liver. *J Crit Care*. 1993;8(3):154–60.
162. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. *Gastroenterol Clin Biol*. 2002;26(10):842–7.
163. Navasa M, et al. Hemodynamic and humoral changes after liver transplantation in patients with cirrhosis. *Hepatology*. 1993;17(3):355–60.
164. Therapondos G, et al. Cardiac morbidity and mortality related to orthotopic liver transplantation. *Liver Transpl*. 2004;10(12):1441–53.
165. Liu H, Lee SS. What happens to cirrhotic cardiomyopathy after liver transplantation? *Hepatology*. 2005;42(5):1203–5.
166. McAvoy NC, et al. Prevalence of coronary artery calcification in patients undergoing assessment for orthotopic liver transplantation. *Liver Transpl*. 2008;14(12):1725–31.
167. Martin P, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144–65.
168. Yao FY, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology*. 2008;48(3):819–27.
169. Azarbal B, et al. Feasibility and safety of percutaneous coronary intervention in patients with end-stage liver disease referred for liver transplantation. *Liver Transpl*. 2011;17(7):809–13.
170. Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. *Liver Transpl*. 2012;18(8):881–91.
171. Kochar R, Nevah Rubin MI, Fallon MB. Pulmonary complications of cirrhosis. *Curr Gastroenterol Rep*. 2011;13(1):34–9.
172. Swanson KL, et al. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. *Am J Transplant*. 2008;8(11):2445–53.
173. Fix OK, et al. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. *Liver Transpl*. 2007;13(6):875–85.
174. Ashfaq M, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. *Am J Transplant*. 2007;7(5):1258–64.
175. Hollatz TJ, et al. Treatment with sildenafil and treprostinil allows successful liver transplantation of patients with moderate to severe portopulmonary hypertension. *Liver Transpl*. 2012;18(6):686–95.
176. Torregrosa M, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. *J Hepatol*. 2005;42(1):68–74.
177. Henderson JM, et al. High cardiac output of advanced liver disease persists after orthotopic liver transplantation. *Hepatology*. 1992;15(2):258–62.

Kia Saeian, Akshay Kohli, and Joseph Ahn

## Abstract

In this chapter, we will review some of the associated complications of portal hypertension including bleeding from esophageal and gastric varices, the development of portal vein thrombosis and its associated implications as well as the very interesting entity of ascites associated intra-abdominal hypertension along with options for management of all these entities with a particular focus implications for the critical care provider.

## Keywords

Variceal hemorrhage • Hepatic venous pressure gradient • Portal vein thrombosis • Cavernous transformation • Intraabdominal hypertension

## 10.1 Introduction

Portal hypertension is a common clinical syndrome defined by a pathologic increase of portal venous pressure which, in turn, leads to an increase in gradient between the portal venous pressure and the hepatic venous or in effect, the inferior vena cava pressure (hepatic venous pressure gradient or HVPg). The increased portal pressure leads to splenomegaly, growth of an extensive network of portal-systemic collaterals that shunt portal blood flow to the systemic circulation bypassing the liver, and development of a hyperkinetic circulatory state. The upper normal value of HVPg is 5 mmHg and PHT becomes clinically significant when this gradient reaches 10 mmHg or higher manifested by ascites, esophageal varices, hepatorenal syndrome etc. Variceal bleeding is typically seen with HVPg  $\geq$  12 mmHg.

K. Saeian, M.D., M.S. (✉)  
Department of Medicine, Medical College of Wisconsin,  
Milwaukee, WI 53226, USA  
e-mail: [ksaeian@mcw.edu](mailto:ksaeian@mcw.edu)

A. Kohli, M.B.B.S.  
Maulana Azad Medical College, Delhi University, Delhi, India  
e-mail: [akshayk1@gmail.com](mailto:akshayk1@gmail.com)

J. Ahn, M.D., M.S., F.A.A.S.L.D.  
Oregon Health & Science University, Portland, OR, USA  
e-mail: [Ahnj@ohsu.edu](mailto:Ahnj@ohsu.edu)

Over 90% of portal hypertension in the western world is attributed to cirrhosis. Portal hypertension in cirrhosis is caused by a combination of two simultaneously occurring hemodynamic processes [1]: Increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis and regenerative nodules, and [2] increased splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed which is a dynamic and thus a modifiable component.

The hypertensive portal circulation naturally decompresses by diverting up to 90% of the portal flow through portosystemic collaterals back to the heart, resulting in flow mediated remodeling and enlargement of these vessels. Vascular endothelial growth factor (VEGF), nitric oxide (NO)-driven VEGF type II receptor expression, and platelet-derived growth factor drive this process. Portal hypertensive bleeding may be related to the development of esophageal or gastric varices but may also manifest as portal hypertensive gastropathy or rarely ectopic variceal development throughout the remainder of the gastrointestinal tract. Variceal rupture occurs when the wall tension exceeds the elastic limits of the variceal wall. Variceal bleeding is the last step in a chain of events initiated by an increase in portal pressure, followed by the development and progressive dilation of varices until rupture and bleed.



## 10.2 Epidemiology

Overall, approximately 40% of patients with histologically confirmed cirrhosis have varices with the rate higher in those with established ascites [1]. An estimated 5–15% of cirrhotics per year develop bleeding.

Depending on the severity of liver disease, the frequency of esophageal varices reportedly varies from 30% to 70% in patients with cirrhosis [2–4] with 9–36% of patients have what are known as “high-risk” varices. Esophageal varices (EV) develop in patients with cirrhosis at an annual rate of 5–8%, but these varices are large enough to pose a risk of bleeding in only 1–2% of cases. Approximately 5–30% of patients with small varices will develop large varices each year and will therefore be at risk of bleeding [2, 5–7].

The rate of development of varices in patients with cirrhosis has not yet been studied thoroughly. In a prospective study, 206 cirrhotic patients (113 without varices and 93 with small esophageal varices) were evaluated during a mean follow up of  $37 \pm 22$  month. The incidence of EV was 12% (5.6–18.4%) at 1 year and 28% (21.0–35.0%) at 3 years [2].

The mortality rate from bleeding esophageal varices in cirrhotics is historically as high as 30–60% but has significantly decreased in the past few decades with recent studies suggesting a 6-week mortality after the first variceal bleeding episode of roughly 15–20% [8, 9]. In a retrospective French report of undifferentiated ICU admitted cirrhotics with variceal bleeding comparing the years 1985 and 2000, there was a significant in-hospital mortality reduction from 42.6% in 1985 to 14.5% in 2000 ( $P < 0.05$ ), reduced re-bleeding rate from 47% to 13%, and reduced bacterial infection rate from 38% to 14% [10]. A systematic review of 12 studies found out that a reduction of hepatic vein pressure gradient to  $\leq 12$  mmHg was associated with a significant reduction in risk of variceal bleeding and mortality [11]. Another study done to evaluate the relationship between the HVPG and formation of and bleeding from varices noted that the patients with endoscopic evidence of varices had a gradient above 12 mmHg while none of those with bleeding varices had a gradient below 12 mmHg, with a mean gradient in bleeding varices being 20.4 mmHg [12]. Unfortunately, it is not feasible nor is it standard practice to obtain portal pressure readings at most centers in the setting of acute bleeding. Thus unless the patient already has these measures established, portal pressures are not typically used in the acute clinical setting to direct initial management.

## 10.3 Patient Evaluation Overview

### 10.3.1 Initial Evaluation

The initial evaluation of a patient with a suspected clinically significant acute upper GI bleed begins with a standard

history, physical examination, laboratory tests including complete blood count, electrolytes including renal and liver functions and coagulation panel to include for risk stratification. We do not currently recommend routine nasogastric lavage. The goal of the initial evaluation is to assess the severity of the bleeding, stratify patient risk which is particularly important in patients with portal hypertension and undertake appropriate resuscitative measures. If portal hypertension is suspected, after rapid stabilization, preferably in an ICU setting with a low threshold for intubation as well as securing adequate intravenous access and rapid volume resuscitation, urgent endoscopy with therapeutic intent should be undertaken.

#### 10.3.1.1 Differential Diagnosis

In the setting of acute upper gastrointestinal (GI) hemorrhage in a patient with cirrhosis with suspected portal hypertension, 60–65% of the cases will be due to esophageal or gastric varices. Patients with portal hypertension remain at risk for other causes of upper G.I. bleeding beyond variceal bleeding including esophagitis, peptic ulcer disease, Mallory Weiss tears, portal hypertensive gastropathy, gastric antral vascular ectasia (GAVE), malignancy and Dieulafoy lesions.

#### 10.3.1.2 Risk Stratification

Initial risk stratification is often dependent on clinical patient factors with a number of higher risk factors that have been established dependent on findings upon endoscopic evaluation. As noted above, measurement of the HVPG is not universally available, and thus other criteria are often used. If the patient is thought to have portal hypertension, then they should be treated as a patient with high risk acute upper G.I. bleeding.

Factors useful in predicting the risk of variceal hemorrhage in patient with cirrhosis include:

- Location
- Size
- Appearance of varices
- Clinical features of patient
- Variceal pressure

The endoscopic assessment of esophageal and gastric varices is of paramount importance in risk stratification and management. It is now recommended that a simplified grading system defining small and large varices be used rather than the previous multilevel grading systems. The term small and large should be by semi-quantitative morphological assessment or by quantitative size estimation with a suggested cut-off diameter of 5 mm, with large varices being those  $>5$  mm. This measurement should be taken with adequate insufflation to avoid size overestimation. Varices that are considered large typically require intervention whereas



**Fig. 10.1** Large esophageal varices with high risk stigmata



**Fig. 10.2** Large esophageal varices with *red wale marks*

those that are considered small can be monitored. Varices are considered adequately eradicated if they completely flatten with insufflation. The presence or absence of high-risk stigmata is also important when assessing those at increased risk of variceal hemorrhage (Figs. 10.1 and 10.2). These stigmata [2] include:

- Red wale marks
- Cherry red spots
- Hematocystic spots
- Diffuse erythema.



**Fig. 10.3** Large Isolated fundic gastric varices

Esophageal varices at the gastroesophageal junction are most likely to rupture as they have the thinnest layer of supporting tissue. This rupture risk follows LaPlace's Law (Wall tension = pressure gradient  $\times$  radius/wall thickness). It follows then that larger varices and those that have a thinner wall are at an increased risk of bleeding. Interestingly, gastric varices which are present in approximately 17% of patient with cirrhosis [13], bleed less frequently than esophageal varices but their management is more difficult and is associated with a higher mortality rate reportedly as high as 45%. The most accepted and well known classification for gastric varices is the Sarin classification in which they are classified per their location and contiguity or lack thereof with other varices:

- Type 1 gastroesophageal varices (lesser curvature varices also called GOV1) ~75%
- Type 2 gastroesophageal varices (greater curvature varices also called GOV2) ~21%
- IGV1 are isolated gastric varices that are limited to the fundus of the stomach and have no contiguity with esophageal varices; ~4% (Fig. 10.3)
- IGV2 are isolated gastric varices that are in other areas of the stomach; ~1%

In a study comparing gastric and esophageal varices, it was found that gastric varices bled in significantly fewer patients but once bleeding ensued, mortality was much more likely in those with gastric variceal bleeding with higher mean transfusion requirements ( $4.8 \pm 0.6$  vs.  $2.9 \pm 0.3$  transfusion units per patient, respectively) (13).

Although the size of varices and the presence of red color signs on the variceal wall are well recognized by most investigators in assessing the risk of variceal hemorrhage, prognostic indexes such as the NIEC index which incorporates the endoscopic signs with clinical data such as the Child Pugh score, can also reliably predict the risk of first bleeding [14]. Variceal pressure can be measured accurately and non-invasively with a pressure-sensitive endoscopic gauge [15]. A prospective cohort study assessing the significance of variceal pressure measurement for prediction of a first variceal bleed concluded that variceal pressure is an important predictor of first variceal bleed [16]. Clinically however this approach has not been widely adopted.

The degree of liver dysfunction is an important predictor of variceal hemorrhage. The Child Pugh classification is an index of liver dysfunction based upon serum albumin concentration, total bilirubin level, prothrombin time, and the presence of ascites and encephalopathy. A higher score in this classification scheme is associated with a higher likelihood of variceal bleeding.

A history of a previous variceal bleeding predicts a high likelihood of subsequent bleeding. More than 70% of patients experience further episodes of variceal bleeding after the index bleed. As a rule of thumb, approximately 1/3 will rebleeding within 6 weeks and another 1/3 will rebleeding after 6 weeks. The risk of rebleeding is greatest in the first 48 h after the index episode and subsequently declines.

### 10.3.1.3 Management of Acute Variceal Bleeding

There are two phases in the management of varices acute phase which involves the management of the acute, active bleeding and the later phase in which there is a focus on prevention of recurrent bleeding [17]. In contrast to patients with non-variceal upper GI bleeding, only 50% of patients with variceal hemorrhage stop bleeding spontaneously. After the cessation of initial hemorrhage, the risk of rebleeding is extremely high during the first 6 weeks. It subsequently declines and later, the risk returns to baseline levels (i.e. equals that of patients who have never bled) [14].

### 10.3.1.4 Special Considerations

The principal complications that can cause death in addition to bleeding include aspiration pneumonia, sepsis, acute on chronic liver failure, hepatic encephalopathy and renal failure. Efforts focused on avoiding and managing these complications are integral to the care of the patient with acute variceal bleeding.

### 10.3.1.5 Airway Protection

Many endoscopists, due to concern about the higher aspiration risk of cirrhotics (reported to be 2.4–3.3% during endoscopy) particularly in light of the high prevalence of hepatic

encephalopathy and the large volume of bleeding, request endotracheal intubation prior to endoscopy. Interestingly however, a retrospective study comparing hospitalized patients with acute variceal bleeding who had elective intubation to those without elective intubation showed worse outcomes in the intubated group. The reasons for this are not fully clear as there may have been a selection bias inherent in a retrospective study or intubation skill may have played a role [18]. Nevertheless, current practice still suggests that elective intubation should be considered, particularly in encephalopathic patients unable to protect their airway. Whether the placement of a nasogastric tube prevents aspiration has not been studied well but we currently do use pre-procedural erythromycin to facilitate gastric emptying and avoid use of initial nasogastric tubes.

### 10.3.1.6 Restricted Resuscitation

A natural tendency to proceed with transfusion should be tempered by the potential that over-transfusion leads to elevated portal pressures which may exacerbate or reinitiate portal hypertensive bleeding. A recent large randomized controlled trial of 889 patients admitted with gastrointestinal bleeding were randomized to a liberal transfusion arm in which blood was transfused when the hemoglobin level dropped to 9 g/dL, or a restrictive transfusion arm in which blood was transfused only when the hemoglobin level dropped to 7 g/dL. In this study, 190 were found to have esophageal variceal bleeding were included and monitored for 45 days. Those cirrhotics receiving the restrictive transfusion strategy had a more favorable outcome regardless of Child's class by a more than 2:1 margin, 12–22% [19]. For similar reasons, overaggressive fluid resuscitation should be avoided in this population.

### 10.3.1.7 Recombinant Factor VIIa

Small pilot studies have shown that recombinant human factor VIIa (rFVIIa) has been associated with improvement or normalization of serum prothrombin time and control of bleeding in patients with evidence of coagulopathy [20–23]. But there have been other studies which have failed to show any clear benefit of recombinant factor VIIa in active variceal bleeding [24, 25]. Before further evaluation confirms benefit, rFVIIa cannot yet be recommended for routine clinical use.

### 10.3.1.8 Antibiotics and Infections

Bacterial infections are present in nearly 20% of patients with cirrhosis who are hospitalized for GI bleed and another 50% develop an infection while hospitalized [26]. A systematic review of eight trials concluded that antibiotic prophylaxis for cirrhotic inpatients with gastrointestinal bleeding is efficacious in reducing the number of deaths and bacterial infections, are well tolerated, and should be advocated [26].



Multiple other studies have shown that antibiotic prophylaxis in these patients is associated with an overall reduction in infectious complications and decreased mortality [27–30]. Antibiotic prophylaxis after endoscopic therapy has been found to prevent rebleeding in patients with acute variceal hemorrhage [31]. However, the choice, duration and selection of patients who will benefit the most still remain unclear.

It has been found that patients with a Child-Pugh's class C and/or a rebleeding are a subgroup of cirrhotic patients with a high risk of infection after gastrointestinal hemorrhage and thus prophylactic treatment with systemic antibiotic is very effective in preventing bacterial infections [29]. The choice, duration and selection of other patients who will benefit significantly remain unclear but typically intravenous ceftriaxone or fluoroquinolones is utilized in patients with portal hypertension and hemorrhage, including even those without ascites [29].

### 10.3.1.9 Vasoactive Medications

The options include the anti-diuretic hormone analogues such as vasopressin and terlipressin (not available in the United States) and somatostatin analogues such as octreotide. Octreotide is very well tolerated and is commonly used in the United States but vasopressin is typically avoided due to its multiple potential adverse outcomes including mesenteric and peripheral ischemia, myocardial infarction, and arrhythmias. Terlipressin is the only agent to have shown a reduction in mortality in single studies or meta-analysis, but is unavailable in the United States [32]. A 2002 meta-analysis comparing somatostatin analogues in addition to endoscopy compared to endoscopy alone for acute variceal bleeding evaluated eight randomized trials with a total of 939 patients found that combination therapy resulted in a significant improvement in early hemostasis but no difference in mortality or adverse events [33]. The use of vasoactive agents is associated with a significantly lower risk of 7 day mortality, and a significant improvement in hemostasis, lower transfusion requirements and a shorter duration of hospitalization [34]. Octreotide is advised with a 50 µg bolus followed by a 50 µg/h intravenous infusion immediately and then extended to 3–5 days if variceal bleeding is confirmed endoscopically [35]. Nonselective beta-blocker therapy has no role in the setting of acute variceal bleeding.

Hepatic encephalopathy—Management of hepatic encephalopathy should not only include lactulose, but should also be accompanied by an aggressive search for potentially reversible factors other than GI bleeding that may be contributing to the encephalopathy. Hypokalemia, for example can promote the development of hepatic encephalopathy via increased renal ammonia production [36]. Similarly metabolic alkalosis may also contribute to the movement of ammonia across the blood brain barrier.

### 10.3.1.10 Renal Failure—Appropriate Volume Replacement, Avoidance of Aminoglycosides and Mismatched Transfusions Are All Important in Minimizing the Risk of Renal Failure

Miscellaneous—Alcoholics should be monitored for withdrawal symptoms and should be administered thiamine. It has been found that these patients, especially those who are nutritionally depleted may develop hypophosphatemia and hypokalemia after dextrose infusions which lead to increase in serum insulin concentrations which in turn derives both phosphate and potassium into the cells [37]. Thus it is important that these issues be kept in mind while managing such patients.

### 10.3.1.11 Endoscopy

It is typically recommended that endoscopy be undertaken within 12 h of presentation [35] after adequate resuscitation and if necessary, intubation has been undertaken. Options for management of active esophageal variceal bleeding endoscopically include endoscopic variceal band ligation (EVL) or endoscopic sclerotherapy (EVS). Endoscopic variceal sclerotherapy has fallen out of favor in part due to its significant side effect profile which includes not only chest pain but also esophageal stricture formation, portal vein thrombosis, possible perforation or embolization, bacteremia as well as ulceration. While EVL does carry a risk for chest pain, eventual esophageal stricture formation as well as ulceration and rebleeding, it is overall much better tolerated and is now carried out as the standard endoscopic therapy on a routine basis. Overall, most studies have shown equivalent rates of endoscopic hemorrhage control with EVL and EVS. There is some data including a study of 179 cirrhotics with acute esophageal variceal bleeding all of whom are treated with vasoactive medications and received either EVL or EVS within 6 h of admission that EVL was superior in terms of bleeding cessation (4% vs. 15%,  $p = 0.02$ ), serious side effects (4% vs. 13%,  $p = 0.04$ ) and 6-week survival (83–67%,  $p = 0.01$ ) [38]. Also the number of endoscopic sessions required to achieve variceal obliteration has been found to be lower with ligation an important measure in prevention of recurrent bleeding [39]. Despite improvements in endoscopic therapy, either early rebleeding or failure to control bleeding occurs in up to 20% of patients with esophageal varices and 40% of patients with gastric varices. A number of rescue therapies are available and should be explored to depending on center expertise.

A commonly used and very effective option to control persistent variceal hemorrhage is placement of a transjugular intrahepatic portosystemic shunt (TIPS) by an experienced interventional radiologist. During TIPS placement, a

polytetrafluoroethylene covered stent is used to connect branches of the hepatic veins (typically on the right) and the portal vein resulting in a diminished HVP (not always normalized). A TIPS may also be indicated in patients with recurrent bleeding or those with refractory ascites. Shunting of unfiltered portal venous flow to the systemic circulation by the TIPS may exacerbate hepatic encephalopathy, so caution needs to be exercised. In addition, TIPS is also contraindicated in patients with high Model for Endstage Liver Disease (MELD) scores and other conditions such as significant pulmonary hypertension or heart failure, or may not be feasible in those with complete and extensive portal venous thrombosis.

A temporizing but more widely available rescue therapy is balloon tamponade and it is effective at controlling bleeding in most cases of variceal bleeding including those with gastric varices (GOV-1 and GOV-2, IGV-1). However, balloon tamponade carries a high rate of complications including esophageal necrosis and rupture. If feasible, it should serve as a bridge to definitive therapy such as TIPS. Endotracheal intubation is mandatory in situations where balloon tamponade is being used.

The options for gastric varices are much more limited endoscopically. Band ligation is not recommended for treatment of gastric varices. There is a very positive experience and success with endoscopic cyanoacrylate glue injection for GOV2 or IGV1 although FDA approval for this in the USA is lacking [40–42]. In those with gastric variceal bleeding and certainly for those with recurrent bleeding, TIPS may be considered early though due to vascular anatomy not all gastric varices may be successfully treated with TIPS. Balloon-occluded retrograde transvenous obliteration (BRTO) of gastric varices is an excellent option as a minimally invasive therapy without the risk of encephalopathy to treat gastric varices and has enjoyed widespread use in Japan since its introduction by Kanagawa in 1996 [43] and is likely superior to endoscopic cyanoacrylate therapy [44].

## 10.4 Portal Vein Thrombosis

### 10.4.1 Introduction

Portal vein thrombosis (PVT) is defined as the occlusion of the lumen of the portal vein (PV) by thrombus formation. PVT is seen most commonly in the setting of portal hypertension from underlying cirrhosis, but is also strongly associated with inherited prothrombotic states as well as acquired conditions such as hepatocellular carcinoma or myeloproliferative disorders. In an autopsy series of 24,000, 1% had PVT, associated with cirrhosis (28%), primary liver malignancy (23%), infection/inflammation (10%), or

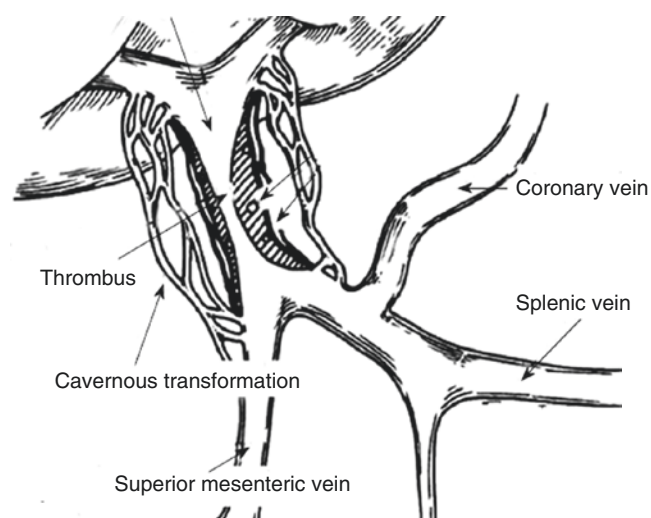
myeloproliferative disorders (3%) [45]. In patients with cirrhosis, the incidence of PVT appears to increase with the severity of underlying liver disease and portal hypertension from ~1% in those with compensated cirrhosis to up to 26% in patients with end-stage liver disease (ESLD) awaiting liver transplantation, with higher rates in those with concomitant hepatocellular carcinoma (HCC) [46–48]. Patients presenting with PVT to the intensive care unit (ICU) present a significant challenge because it poses simultaneous competing risks of mesenteric ischemia and progressive portal hypertension related GI bleeding (GIB) without intervention versus local and systemic complication risks of interventions such as anticoagulation. This section will review the pathology, presentation, and optimal management of patients with PVT.

### 10.4.2 Pathology

Portal vein thrombosis can be categorized into acute versus chronic PVT, with further sub-categorization by degree of occlusion (partial vs. complete), extension or involvement of other splanchnic veins, and by the presence of infection, underlying cirrhosis, or malignancy. The differentiation between acute PVT and chronic PVT is challenging because patients with PVT may be asymptomatic, and in the absence of baseline imaging, the acuity of PVT may be difficult to substantiate. This has led to heterogeneity in definition of acute versus chronic PVT in research studies on PVT, and thus has limited the refinement of evidence based management of PVTs. Nevertheless, a common distinguishing point of differentiation is the absence of or insignificant presence of hepatopetal collateral veins bypassing the PVT on imaging studies in patients with acute PVT and the presence of these collateral veins leading to cavernous transformation or cavernoma in patients with chronic PVT (Fig. 10.4). Other imaging clues include the absence of portal hypertension manifested as splenomegaly and/or abdominal varices. Some authors have suggested that PVT be designated as acute in patients who have had symptoms within 60 days prior to the diagnosis given that 6–60 days is the hypothesized time frame for collateral formation [49].

For both acute and chronic PVT, it is important to note whether the occlusion is incomplete/partial or complete given that partial PVT is more likely to be responsive to intervention. The presence of extension into the superior mesenteric vein (SMV) is critical to note because the SMV involvement denotes a higher risk of subsequent intestinal ischemic complications and multiorgan failure. This is reflected in the most commonly used classification system [50] (Table 10.1). In the patient presenting with PVT and symptoms of sepsis or infection or with concomitant abdom-





**Fig. 10.4** Cavernous transformation or cavernoma

**Table 10.1** PVT classification system

Grade	Description
1	Partially thrombosed PV, <50% of lumen, with or without extension into the SMV
2	>50% occlusion of the PV (including total PV occlusion) with or without extension into the SMV
3	Complete thrombosis of both the PV and proximal SMV (Distal SMV open)
4	Complete thrombosis of the PV and both the proximal and distal SMV

Yeredel, Tx 2000; 69:1873

inal infections such as diverticulitis, cholecystitis, appendicitis, or pancreatitis, the presence of infected PVT must be distinguished from noninfected PVT given its ramifications on antibiotic need and duration [51]. Finally, PVT is most commonly further categorized by the presence of cirrhosis as well as malignancy, most commonly hepatocellular carcinoma (HCC). For management purposes, the acuity of PVT, extension into the mesenteric veins and presence of cirrhosis are the most important factors in guiding anticoagulation decision making.

Pathophysiologically, acute PVT leads to an initial compensatory arterial rescue with hepatic artery vasodilation to maintain hepatic blood inflow. Secondary compensatory venous rescue occurs with the formation of collateral veins to bypass the occluded portion of the PV. This is the process by which cavernous transformation or cavernoma occurs [52]. In the ICU setting, acute PVT may lead to ischemic hepatitis, especially if there is concomitant systemic hypotension or shock. Complications can occur with the extension of the PVT to the SMV leading to intestinal ischemia with lactic acidosis, and multiorgan failure. Longer-term complications of acute PVT include

progression to chronic PVT and development of portal hypertension with formation of varices in the esophagus and stomach, as well as other atypical sites. A rare but often overlooked complication is portal biliopathy or cholangiopathy which is caused by the development of enlarged collateral veins from the PVT near the common bile duct called the Plexus of Petren, leading to compression of the biliary system, subsequent obstruction, and cholangitis. Most patients are asymptomatic but some patients develop biliary complications such as pruritus, jaundice, cholangitis, and secondary biliary cirrhosis [53, 54].

Risk factors for PVT are similar to well-known Virchow's triad of risk factors for venous thromboembolism (stasis, hypercoagulability and endothelial injury), and are notable that multiple risk factors are often present. However, no risk factors for PVT are found in up to 25–30% of presentations [55, 56]. Hypercoagulable states due to inherited prothrombotic conditions such as factor V Leiden deficiency, prothrombin gene mutations and acquired conditions such as antiphospholipid antibody syndrome, myeloproliferative disorders associated with JAK2 mutations must be considered in PVT evaluation. Other well-known risk factors include stasis or reduction in portal venous flow due to cirrhosis or advanced liver disease, Budd-Chiari syndrome, or via direct vascular invasion or compression due to HCC or cholangiocarcinoma. Finally, local injury leading to endothelial activation of prothrombotic factors by intraabdominal inflammatory or infectious states such as pancreatitis, cholecystitis, inflammatory bowel disease, or infections are reported in up to 10% of PVT cases [56].

### 10.4.3 Presentation and Diagnosis

Patients presenting with PVT in the ICU may not be able to give much history due to their critically ill state, or may provide only nonspecific complaints of generalized abdominal pain, nausea, malaise, or anorexia. They may only have nonspecific exam findings of the predisposing conditions that led to the PVT, such as cirrhosis, intraabdominal infectious or inflammatory states (diverticulitis, appendicitis, pancreatitis, etc.). Liver function tests may be normal in chronic PVT, but may be nonspecifically elevated in ICU patients with acute PVT, again driven by the primary process such as shock, ischemia or subsequent multiorgan failure. Thus, an index of suspicion must be maintained for PVT, especially in patients who are predisposed to their formation such as those with cirrhosis, primary or secondary hepatic malignancies, intraabdominal inflammatory/infectious entities, and patients with prothrombotic conditions. Imaging revolves around ultrasound and CT scans in the ICU, with the PVT often diagnosed incidentally or unexpectedly in the process of evaluation of nonspecific presentation scenarios. Imaging

evaluation should include assessment for chronicity, degree of occlusion, extension into the SMV or splenic vein, and the presence of cirrhosis or malignancy. Confirmation of PVT should be followed by a systematic evaluation for the presence of a hypercoagulable state, especially for patients with acute PVT without underlying liver disease.

In the ICU setting, PVT can be separated into whether the PVT is the primary driver of the patient's presentation or is an incidental finding that may complicate management. Primary ICU presentations include pylephlebitis, mesenteric vein thrombosis, portal hypertension related gastrointestinal bleeding, and portal biliopathy. Secondary, or incidental ICU presentations include the presence of acute or chronic PVT found on imaging in patients with abdominal trauma, ruptured HCC, or abdominal pain.

Patients with acute PVT extending into the SMV may develop mesenteric ischemia and nonspecific symptoms of severe abdominal pain, diarrhea, nausea and vomiting [56]. Liver function tests may be increased due to secondary ischemic hepatitis due to the reduced blood inflow to the liver, and the systemic sequela of abdominal ischemia. Although liver ultrasound (US) with Doppler is useful due to its near ubiquitous availability, relatively low price point, and noninvasive and thus repeatable nature, it is limited in its usefulness in determining the extent of the PVT, involvement of the SMV, as well as in assessing for the presence of underlying predisposing risk factors [57, 58]. In addition, due to its operator dependent nature as well as reduced diagnostic value in those with significant obesity, abdominal girth, ascites, or bowel gas, a negative US should be followed by consideration of a CT scan for pursuit of SMV involvement in those with PVT with suspected mesenteric ischemia. CT is more useful in evaluating the anatomy of the splanchnic vasculature, in assessing the status of other abdominal organs, in looking for predisposing conditions such as cirrhosis or HCC, and in detecting complications such as bowel infarction or abscess formation [59]. MRIs have comparable sensitivity as CT scans, and may be an alternative if CT scans are not feasible or not preferred, such as in avoiding radiation in young patients or pregnant patients [60]. However, although MRI/MRCP may be superior in assessing for the presence of portal biliopathy than CT, its practical utilization in the ICU may be limited due to reductions in resolution and definition in patients with significant ascites or in ICU patients who may be unable to tolerate the time and instructions for optimal MRI scanning [61]. If SMV thrombosis is noted, intestinal infarction must be considered especially if there are imaging findings of intestinal wall thinning, lack of intestinal wall enhancement and laboratory findings of lactic acidosis and multiorgan failure.

Presentation of pylephlebitis or suppurative, inflamed thrombosis of the PV can include the nonspecific signs and symptoms of abdominal sepsis. Patients may have severe abdominal pain, nausea, vomiting, fever, chills, and malaise along with features of an acute abdomen depending on the underlying source of the infection and inflammation, most commonly diverticulitis, appendicitis, cholecystitis, and pancreatitis. Because the signs of shock and infection are nonspecific, a high index of suspicion must be maintained for the presence of pylephlebitis. Although US can be used to diagnose a PVT, an abdominal CT is more useful in confirming the PVT and also concomitantly assessing for the underlying source of the primary infection or inflammation. Positive blood cultures, usually of polymicrobial or *Bacteroides fragilis* species along with the PVT imaging confirmation helps to make the diagnosis of pylephlebitis.

PVT related GIB are seen in the setting of chronic PVT and cavernous transformation, and present with gastroesophageal variceal bleeding, as described in the previous sections of this chapter. Patients who develop acute PVT in the setting of underlying cirrhosis with existing portal hypertension may also present with gastroesophageal variceal bleeding. This is why patients who present with portal hypertension related GIB should be screened for PVT, underlying cirrhosis, and HCC.

#### 10.4.4 Management

Both patients with PVT as the primary driver of ICU admission as well as those with incidental findings of PVT unrelated to the primary ICU admission can pose a management challenge by raising the issue of anticoagulation (AC). ICU patients tend to be less ideal candidates for anticoagulation than non-ICU patients, and may have higher perceived risks of intervention with anticoagulation. Nevertheless, the primary goal of PVT management is to identify and treat not only the PVT itself towards recanalization of the PV, but also to address the predisposing conditions that led to the PVT. This involves appropriate selective prolonged antibiotic management for conditions such as pylephlebitis, diverticulitis and surgical management of appendicitis, cholecystitis, and other conditions that pose risk for PVT development. Patients with PVT related portal biliopathy/ cholangiopathy may present with obstructive cholangitis, and should be managed similarly as choledocholithiasis cases, with endoscopic retrograde cholangiopancreatography along with intravenous antibiotics.

Secondary goals are to prevent the complications that may occur with PVT progression such as portal hypertension related GIB, mesenteric ischemia, and ischemic hepatitis.

Prevention of the extension of the PVT into the SMV is important not only for the sake of reducing the risk of intestinal ischemia but because in liver transplant candidates, SMVT may preclude candidacy.

The challenge in ICU patients with PVT is to balance simultaneously the risk of GIB versus recurrent or progressive thrombosis with anticoagulation. Anticoagulation is a sharp tool, and can be associated with significant morbidity and mortality. Thus, patients must be assessed for their underlying risk factors for PVT as outlined above, triaged for timing of consideration for recanalization, and stratified by the risks and benefits of anticoagulation. The rationale for anticoagulation in PVT is that spontaneous recanalization, especially of complete or extensive PVT is unlikely. Anticoagulation can also help ameliorate symptoms and reduce morbidity by reducing the risk of ischemia, SMV thrombosis, progression to chronic PVT, recurrent thrombosis associated with hypercoagulable states, and esophageal variceal bleeding. It can also help maintain candidacy for liver transplantation. The rationale for withholding anticoagulation is based on the assessment that the immediate risk of complications is greater than the potential benefits, such as in patients presenting with GIB. However, in the absence of overt contraindications, anticoagulation should be considered.

Risk stratification with esophagogastroduodenoscopy (EGD) should be instituted in patients with chronic PVT who are at risk for having formed gastroesophageal varices that may pose an increased risk of GIB with anticoagulation. Patients with acute PVT without underlying cirrhosis or advanced hepatic fibrosis do not require mandatory screening with EGD given the low risk of underlying varices. Patients found to have small esophageal varices (EV) can proceed with anticoagulation. Those with medium EV can be placed on prophylaxis with nonselective beta-blockers while patients with large esophageal varices especially with high bleeding risk signs can be managed with esophageal band ligation and/or beta-blockers to reduce the risk of anticoagulation associated GIB [62]. If band ligation is initiated, AC can typically be considered after 2 weeks post-banding, to reduce the risk of banding ulcer bleeding [63]. The key is to assess the patient's risk of bleeding on AC versus the patient's risk of thrombotic events or progression of PVT off it.

Data on the timing of AC is limited, but suggests that if AC is considered, it should be started as soon as possible after the indications are confirmed and the risks have been ameliorated. A therapeutic window may exist where with increased time from acute PVT, the recanalization rates begin to diminish [52, 63, 64]. The duration of anticoagulation has traditionally been at least 3–6 months in the absence

of a chronic prothrombotic state and in cases with a reversible or self-limited risk factor. Patients with prothrombotic states, or involvement of the SMV are recommended for indefinite AC barring any other contraindications [65].

Once the decision to initiate AC has been made, the choice of anticoagulant must be made between heparin, low molecular weight heparin (LMWH), vitamin K antagonist (VKA), and direct acting oral anticoagulants (DAAC). There is no consensus on the superiority of one regimen over the others, due to the lack of data and limitations in the experience of using AC for PVT, especially in patients with chronic liver disease or chronic PVT. In the ICU, heparin may be the most logical initial choice given the often fluid nature of the patient's clinical state, and the need for prompt initiation and discontinuation. LMWH has also been more widely used because of its ease of dosing and lack of requirement for INR monitoring. However, there is limited data for its use in patients with PVT, especially in those with cirrhosis or renal insufficiency who may have fluid overload or edema that may limit absorption from the subcutaneous route. Furthermore, dose adjustments may be needed in patients with renal dysfunction and monitoring with anti-Xa activity may be unreliable, especially in those with cirrhosis [66, 67].

The Vitamin K antagonist warfarin has been traditionally used for PVT after initiation and bridging with LMWH, for longer term PVT management. However, in the ICU setting, the role for VKA initiation may be limited. If considered, it would for patients in a clinically steady state and selected because of its relative lower cost compared to LMWH and DAAC as well as availability of rapid reversal if needed for FFP. Disadvantages of VKA for PVT include the difficulty of trying to use INR to monitor VKA efficacy in patients with elevated INR at baseline, especially those with cirrhosis. In addition, VKA's effect on the INR, which is a part of the MELD score, can have unintended consequences on the candidacy of patients listed for liver transplantation.

Direct acting anticoagulants which have direct inhibition of thrombin or activated factor Xa such as rivaroxaban or apixaban have not been widely studied in patients with PVT or cirrhosis. Nevertheless, given their convenience due to their fixed dosing, oral formulation, lack of need for lab monitoring of efficacy, and lack of direct impact on the INR or MELD score, there has been growing interest in their use [68, 69]. However, at this point, DAACs are generally not recommended for patients with PVT, especially in the ICU setting due to a lack of large scale studies, as well as the risks due to a lack of an FDA approved antidote (although they are in development), and reports of possible drug induced liver injury [70, 71].

Anticoagulation is advised for acute PVT in patients without cirrhosis by both the American Association for the Study of Liver Disease (AASLD) and American College of Chest Physicians (ACCP) practice guidelines. Multiple studies have reported a 60–90% overall recanalization (both partial and complete) rate and up to 35–45% complete recanalization with AC [56, 72, 73]. Adverse events were reported to be very low (0–5%) with bleeding unrelated to portal hypertension as the main complication [53, 64, 74].

For patients with acute PVT who have underlying cirrhosis, the AASLD recommends a case-by-case approach to consider AC in the setting of a prothrombotic state, SMV thrombosis, and in those patients awaiting liver transplantation. Appropriate risk stratification and mitigation of gastroesophageal variceal bleeding as described above was advised prior to initiating AC. Multiple smaller reports of the safety and efficacy of AC in cirrhotic patients with PVT suggest that with appropriate patient selection, similar but slightly lower recanalization rates as those with non-cirrhotic acute PVT have been reported [71, 75, 76]. Slightly higher risks of AC associated bleeding than in PVT patients without cirrhosis undergoing AC have been reported from a small number of studies [63, 77].

Patients with chronic PVT who are diagnosed with non-correctable prothrombotic disorders or with progressive or extending PVT, especially with symptoms, should be considered for AC provided there are no present contraindications such as recent or active GIB, untreated esophageal varices. In general, patients with chronic PVT and cirrhosis, are considered for AC only in the setting of additional risk factors such as a prothrombotic state or HCC, after appropriate risk reduction of existing esophageal varices have been completed with esophageal band ligation or beta-blocker therapy, and as they await liver transplantation. However, robust data on the rate of adverse events or complications in chronic PVT undergoing AC are not yet available.

The question of thrombolytic therapy comes up not infrequently in the ICU setting for PVT. The idea of aggressive infusion of thrombolytics to burst through PVT to recanalization is appealing. However, the data for thrombolysis is disappointing with low rates of recanalization and notable for high rates of adverse events of bleeding. Whether the approach is by indirect infusion via injection into the superior mesenteric artery or directly into the PV, the risk of bleeding and complications appears to be greater than the potential benefit of expedited recanalization [73, 78]. Thrombolysis for PVT cannot be recommended.

PVT used to be a contraindication to TIPS placement due to the technical difficulty of placing the TIPS in the setting of PV occlusion. There is still no robust data to compare TIPS versus anticoagulation. But recently, there have been multiple reports of successful TIPS placement in the setting of even extensive and chronic PVT [79–82]. These studies are

notable for selection of patients with PVT who were potential liver transplant candidates for whom maintaining patency of the PVT would allow continuation on the liver transplant waiting list. These studies report success in the combination of mechanical thrombectomy and restoration of blood flow through the shunt leading to recanalization even in the absence of systemic AC. Thus, TIPS can be considered in the ICU in the setting of the availability of an experienced interventional radiology team for patients with PVT who present with portal hypertension related GIB and in those who need recanalization to allow maintenance of liver transplant candidacy. The usual TIPS complications remain however, including the risk of technical failure, TIPS dysfunction, and development of TIPS-related hepatic encephalopathy.

Finally, liver transplantation is the definitive therapy for patients with chronic liver disease and PVT. Similarly to the situation with TIPS, PVT used to be a contraindication to liver transplantation, until as recently as 1985. Refinements in surgical technique, earlier diagnosis, perioperative management have led to successful liver transplantation in patients with PVT. Nonetheless, growing evidence suggests that although PVT is not a marker for increased wait list mortality, it has a negative impact on 1-year survival after liver transplantation [47, 83–86]. In the ICU in the immediate post-transplant period, close follow up of PVT with an ultrasound in the first week is usually performed. Short term AC has been reported after liver transplantation, but has not been studied or compared to the use of antiplatelet agents which have been reported to be used at low doses.

Overall, there is very limited data on the long-term management outcomes or prognosis of patients presenting with PVT. However, patients now appear to be presenting at earlier PVT formation stages, due to a wider awareness of PVT and improved diagnostic imaging techniques, improving the possibility of successful intervention through earlier AC consideration resulting in improved overall outcomes. What's clear is that acute PVT is a step along the way to chronic PVT, at which point treatment outcomes, risks, and best practices are less clearly defined. Thus, it is ideal if PVT is treated early, after appropriate risks stratification has been completed. Figure 10.5 outlines a suggested management algorithm for PVT in the ICU.

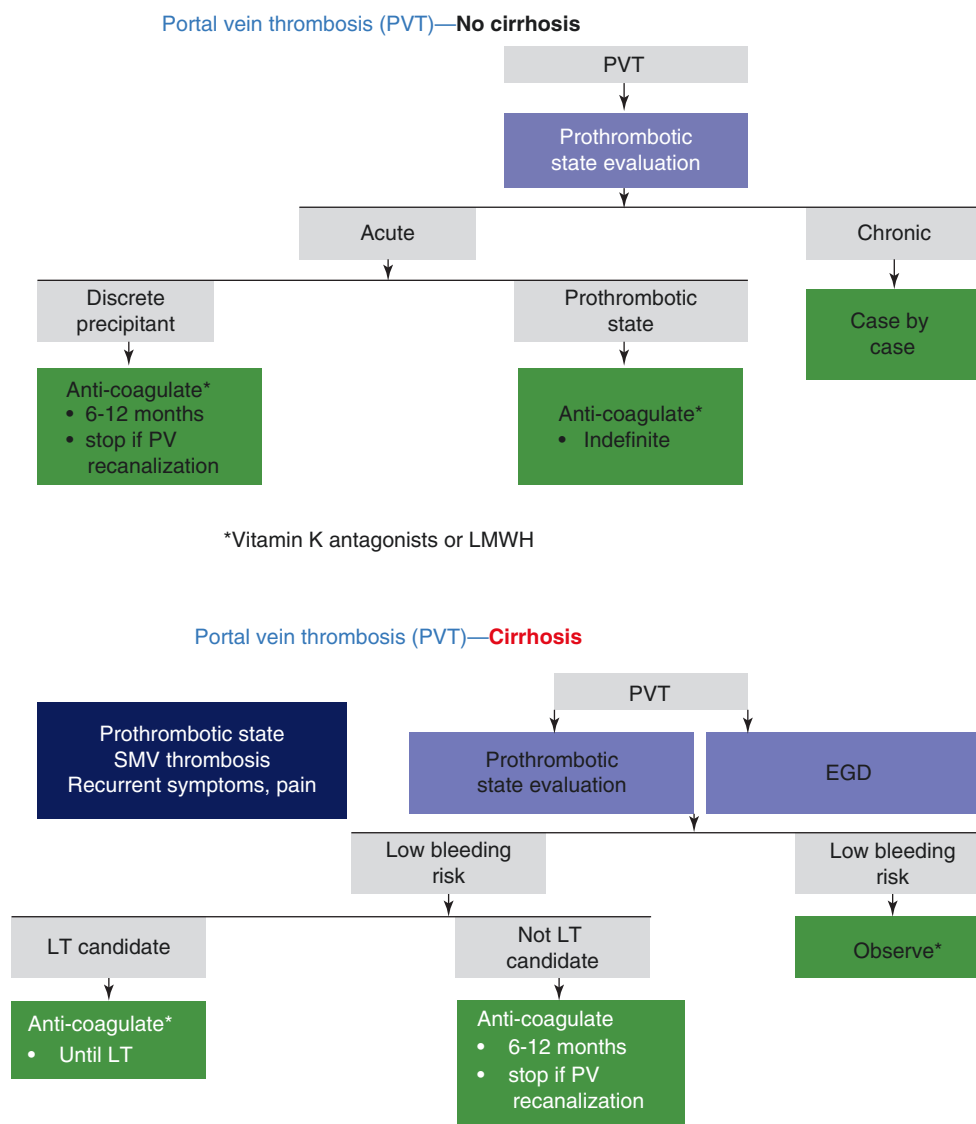
---

## 10.5 Ascites and Intraabdominal Hypertension

### 10.5.1 Introduction

Intraabdominal hypertension (IAH) is defined as the presence of elevated pressure within the abdominal compartment, and leads to abdominal compartment syndrome (ACS). ACS is an entity well known in the surgical specialties, but



**Fig. 10.5** Management algorithm for PVT

less appreciated in the medical intensive care of patients with cirrhosis or ESLD. For example, ACS is well recognized and reported to be present in at least 1% of patients presenting with trauma, but similar data on patients with ascites is not available, and is unknown [87] (Hong). However, failure to recognize ACS from tense ascites, can lead to systemic hypoperfusion, multiorgan failure and an increased risk of death [88–90]. Thus, given its association with poor clinical outcomes, IAH is an important under-recognized entity to be aware of for clinicians taking care of patients with ascites in the ICU.

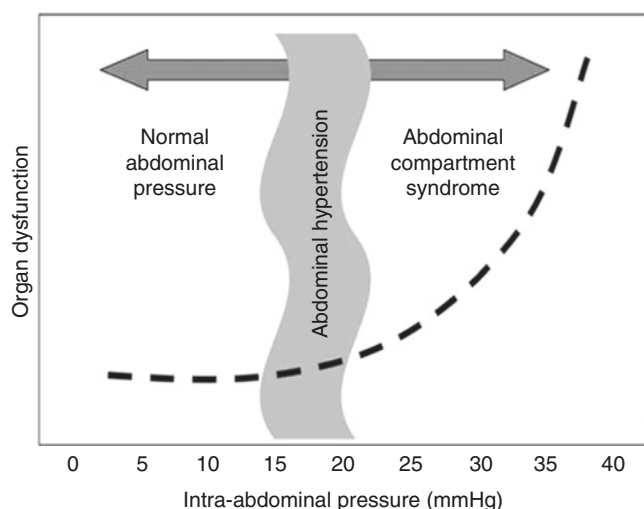
### 10.5.2 Pathology

Intraabdominal hypertension has been defined by expert consensus through the World Society of the Abdominal Compartment Syndrome (WSACS) as a sustained elevation

of intraabdominal pressure (IAP) >12 mmHg (compared to a normal IAP of <5 mmHg) [91]. This definition is commonly used because organ dysfunction often becomes manifested above this pressure. ACS is defined as IAH with a sustained IAP of >20 mmHg, associated with new organ dysfunction or failure with or without abdominal perfusion pressure (APP) of <60 mmHg (where APP = Mean Arterial Pressure – IAP). Clinically however, ACS is defined IAH associated new organ dysfunction without a strict IAP threshold due to inter-patient variability in IAP values that induce organ failure. Figure 10.6 shows a representation of the spectrum from normal IAP to ACS [92]. IAH has been further classified by the WSACS into four grades and has also been differentiated by the timing of its onset. These categorizations have been outlined in Table 10.2.

Intraabdominal pressure is a reflection of the balance between intraabdominal volume and the abdominal wall compliance. Wall compliance defined as its flexibility to





**Fig. 10.6** Spectrum from normal IAP to IAH to ACS

**Table 10.2** IAH categories

Grade	IAP (mmHg)	
Normal	<12	
I	12–15	
II	16–20	
III	21–25	
IV	>25	
Type	Timing	Example
Hyperacute	Transient, seconds	Sneezing
Acute	Over hours	Trauma, Hemorrhage
Subacute	Over days	Ascites
Chronic	Over months	Obesity, pregnancy

yield elastically when force is applied, is increased in patients with chronically enlarged girth such as those with obesity, pregnancy, or recurrent ascites [93]. Risk factors for the development of IAH can be primary, due to direct injury or disease process in the abdominal region such as with ascites, trauma, or abdominal surgeries. It can also be secondary, due to conditions that don't originate in the abdomen such as with sepsis, severe burns, and rapid fluid resuscitation [94, 95]. Patients with liver disease can develop IAH in the setting of high volume, rapid resuscitation for shock (septic, hemorrhagic, burns) in the setting of increased abdominal content with ascites or a large HCC [96]. Increasing ascites as the cause of IAH can have detrimental effects on multiple organ systems as summarized in Table 10.3.

### 10.5.3 Presentation and Diagnosis

Patients presenting with ascites to the ICU with IAH may only have nonspecific symptoms of malaise, weakness, lightheadedness, dyspnea, abdominal bloating, or pain.

**Table 10.3** IAH effects on organ systems

Organ system	Mechanism	Clinical outcome
Cardiovascular	Decreased venous return, impaired ventricular compliance and contractility, decreased cardiac output	Hypotension
Pulmonary	Reduced chest wall compliance, reduced spontaneous tidal volumes	Hypoxemia, hypercarbia
Renal	Renal vein compression, renal artery vasoconstriction	Oliguria
Gastrointestinal	Reduced mesenteric blood flow, intestinal edema, hypoperfusion, bowel ischemia, bacterial translocation	Lactic acidosis, sepsis, diarrhea
Hepatic	Reduced portal vein and hepatic artery flow	Ischemic hepatitis
Central Nervous System	Increased intracranial pressure	Mental status changes

These symptoms may be easily missed or misattributed to more evident clinical diagnosis. Some patients may be unable to communicate due to their critically ill state, encephalopathic condition, or from the effects of mechanical intubation or medications. The key is to maintain a high index of suspicion for the possibility of IAH in patients with ascites, who are not the typically recognized patients with ACS such as those with trauma, burns, or in the post-operative state.

Physical examination for IAH is not accurate to detect or diagnose ACS. The observation of a “tense abdomen” from ascites is a poor predictor of ACS [97, 98]. However, clinical observations in the setting of tense ascites such as cardiac instability with hypotension, tachycardia along with increasing ventilator requirements, oliguria, and signs of hypoperfusion such as cool skin, obtundation, restlessness should alert the clinician to the possibility of IAH and ACS. Abdominal imaging in general is not helpful because the findings are not specific to IAH, but can be useful to evaluate for the presence of hemorrhage leading to hemoperitoneum, or other potential intraabdominal causes of clinical decompensation.

IAH can be diagnosed through indirect IAH monitoring which is traditionally performed by an intravesical approach through using a urinary catheter [98]. There is strong correlation between intravesical measurement of bladder pressure and directly measured intraabdominal pressures [99, 100]. Other possible approaches include using intragastric, intracolonic, or IVC catheters, but these are not practical or widely utilized. Typical steps for intravesical measurement of IAP are [92]:

- Clamp foley catheter drainage tube
- Instill 25 cc sterile saline into the bladder via the aspiration port

- Attach pressure transducer into the aspiration port
- Measure pressure at end expiration in the supine position. Zero transducer at the midaxillary line.

Commercial three way stopcocks are available to avoid repeat puncturing of the aspiration port.

### 10.5.4 Management

Management of patients with ascites presenting with IAH is simpler than managing patients in general with ACS because treatment is focused on the relieving the IAP from the ascites and systemic perfusion optimization. Unlike patients with abdominal trauma, post-abdominal surgery, or severe burn states whose management may require surgical decompression to relieve the IAH, patients with ascites can undergo percutaneous evacuation of ascites through therapeutic paracentesis. In fact, large volume paracentesis (LVP) can be both diagnostic and therapeutic for IAH, as improvement of the clinical state of the patient via observation of their cardiac index, urine output, and pulmonary status can be seen if IAH was contributing to the patient's clinical presentation [101, 102]. However, the limitations of LVP in the ICU is that it tends not to be a definitive therapy but a temporizing one, given the often rapid re-accumulation of ascites fluid in patients with cirrhosis or ESLD. Nevertheless, LVP remains the cornerstone in the management of tense ascites and IAH.

Clinicians in the ICU taking care of patients with cirrhosis, end-stage liver disease, or post-liver transplantation must remember that IAH may be more common than is appreciated, and that there is likely underestimation of its prevalence due to a lack of routine IAP monitoring. Early diagnosis and recognition is paramount, to allow timely consideration of LVP and to prevent development of further morbidity and mortality. Given that physical examination findings may not be accurate nor predictive of IAH, a high index of suspicion must be maintained. It is important to recognize that excessive fluid resuscitation for a myriad of common ICU reasons such as bleeding or sepsis can contribute to IAH in patients with ascites, justifying a sense of caution in tempering fluid resuscitation tempos in these vulnerable patients. Finally, when in doubt, paracentesis should be performed in the clinically unsteady patient in the ICU for both evaluation of infection such as spontaneous bacterial peritonitis, and to relieve potential IAH.

## References

1. Ja I, F K. Primary prophylaxis of variceal bleeding. *Gastroenterol Clin North Am.* 2014;43(4):783–94.
2. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol.* 2003;38(3):266–72.
3. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. *J Hepatol.* 2008;48:S68–92.
4. Esophageal varices. | National Guideline Clearinghouse [Internet]. [cited 2017 Mar 23]. Available from: <https://www.guideline.gov/summaries/summary/47781/esophageal-varices?q=+esophageal+varices>.
5. Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology.* 2004;127(2):476–84.
6. Zoli M, Merkel C, Magalotti D, Gueli C, Grimaldi M, Gatta A, et al. Natural history of cirrhotic patients with small esophageal varices: a prospective study. *Am J Gastroenterol.* 2000;95(2):503–8.
7. de Franchis R. Evaluation and follow-up of patients with cirrhosis and oesophageal varices. *J Hepatol.* 2003;38(3):361–3.
8. Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. *Am J Gastroenterol.* 2003;98(3):653–9.
9. Thomopoulos K, Theocharis G, Mimidis K, Lampropoulou-Karatza C, Alexandridis E, Nikolopoulou V. Improved survival of patients presenting with acute variceal bleeding. Prognostic indicators of short- and long-term mortality. *Dig Liver Dis.* 2006;38(12):899–904.
10. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology.* 2004;40(3):652–9.
11. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology.* 2006;131(5):1611–24.
12. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology.* 1985;5(3):419–24.
13. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology.* 1992;16(6):1343–9.
14. de Franchis R, Primignani M. Why do varices bleed? *Gastroenterol Clin North Am.* 1992;21(1):85–101.
15. Bosch J, Bordas JM, Rigau J, Viola C, Mastai R, Kravetz D, et al. Noninvasive measurement of the pressure of esophageal varices using an endoscopic gauge: comparison with measurements by variceal puncture in patients undergoing endoscopic sclerotherapy. *Hepatology.* 1986;6(4):667–72.
16. Nevens F, Bustami R, Scheys I, Lesaffre E, Fevery J. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients. *Hepatology.* 1998;27(1):15–9.
17. Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology.* 1981;80(4):800–9.
18. Koch DG, Arguedas MR, Fallon MB. Risk of aspiration pneumonia in suspected variceal hemorrhage: the value of prophylactic endotracheal intubation prior to endoscopy. *Dig Dis Sci.* 2007;52(9):2225–8.
19. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368(1):11–21.
20. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, González Abraldes J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology.* 2004;127(4):1123–30.
21. Chuansumrit A, Chantarojanasiri T, Isarangkura P, Teeraratkul S, Hongeng S, Hathirat P. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis.* 2000;11(Suppl 1):S101–5.

22. Ejlsers E, Melsen T, Ingerslev J, Andreasen RB, Vilstrup H. Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. *Scand J Gastroenterol*. 2001;36(10):1081–5.
23. Kaliciński P, Kamiński A, Drewniak T, Ismail H, Szymczak M, Markiewicz M, et al. Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. *Transplant Proc*. 1999;31(1–2):378–9.
24. Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. *Hepatology*. 2008;47(5):1604–14.
25. Martí-Carvajal AJ, Karakitsiou D-E, Salanti G. Human recombinant activated factor VII for upper gastrointestinal bleeding in patients with liver diseases. *Cochrane Database Syst Rev*. 2012;3:CD004887.
26. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. *Cochrane Database Syst Rev*. 2002;2:CD002907.
27. Soriano G, Guarner C, Tomás A, Villanueva C, Torras X, González D, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. *Gastroenterology*. 1992;103(4):1267–72.
28. Pauwels A, Mostefa-Kara N, Debenes B, Degoutte E, Lévy VG. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. *Hepatology*. 1996;24(4):802–6.
29. Bernard B, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology*. 1999;29(6):1655–61.
30. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*. 2002;35(1):140–8.
31. Hou M-C, Lin H-C, Liu T-T, Kuo BI-T, Lee F-Y, Chang F-Y, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology*. 2004;39(3):746–53.
32. Ioannou GN, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev*. 2003;CD002147. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002147/abstract>.
33. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruizdel-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology*. 2002;35(3):609–15.
34. Wells M, Chande N, Adams P, Beaton M, Levstik M, Boyce E, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. *Aliment Pharmacol Ther*. 2012;35(11):1267–78.
35. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63(3):743–52.
36. Artz SA, Paes IC, Faloon WW. Hypokalemia-induced hepatic coma in cirrhosis. Occurrence despite neomycin therapy. *Gastroenterology*. 1966;51(6):1046–53.
37. Knochel JP. Hypophosphatemia in the Alcoholic. *Arch Intern Med*. 1980;140(5):613–5.
38. Villanueva C, Piqueras M, Aracil C, Gómez C, López-Balaguer JM, Gonzalez B, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. *J Hepatol*. 2006;45(4):560–7.
39. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med*. 1995;123(4):280–7.
40. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*. 2001;33(5):1060–4.
41. Oho K, Iwao T, Sumino M, Toyonaga A, Tanikawa K. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. *Endoscopy*. 1995;27(5):349–54.
42. Sarin SK, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol*. 2002;97(4):1010–5.
43. Kanagawa H, Mima S, Kouyama H, Gotoh K, Uchida T, Okuda K. Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration. *J Gastroenterol Hepatol*. 1996;11(1):51–8.
44. Hong CH, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Treatment of patients with gastric variceal hemorrhage: endoscopic N-butyl-2-cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration. *J Gastroenterol Hepatol*. 2009;24(3):372–8.
45. Ogren M, Bergqvist D, Björck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. *World J Gastroenterol*. 2006;12(13):2115–9.
46. Okuda K, Ohnishi K, Kimura K, Matsutani S, Sumida M, Goto N, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology*. 1985;89(2):279–86.
47. Ponziani FR, Zocco MA, Senzolo M, Pompili M, Gasbarrini A, Avolio AW. Portal vein thrombosis and liver transplantation: implications for waiting list period, surgical approach, early and late follow-up. *Transplant Rev (Orlando)*. 2014;28(2):92–101.
48. Llovet JM, Bruix J. Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology*. 2000;32(3):679–80.
49. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. *J Hepatol*. 2014;60(2):421–41.
50. Yerdel MA, Gunson B, Mirza D, Karayalçın K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation*. 2000;69(9):1873–81.
51. Kanellopoulou T, Alexopoulou A, Theodossiades G, Koskinas J, Archimandritis AJ. Pylephlebitis: an overview of non-cirrhotic cases and factors related to outcome. *Scand J Infect Dis*. 2010;42(11–12):804–11.
52. Handa P, Crowther M, Douketis JD. Portal vein thrombosis: a clinician-oriented and practical review. *Clin Appl Thromb*. 2014;20(5):498–506.
53. Condat B, Vilgrain V, Asselah T, O'Toole D, Rufat P, Zappa M, et al. Portal cavernoma-associated cholangiopathy: a clinical and MR cholangiography coupled with MR portography imaging study. *Hepatology*. 2003;37(6):1302–8.
54. Harmanci O, Bayraktar Y. How can portal vein cavernous transformation cause chronic incomplete biliary obstruction? *World J Gastroenterol*. 2012;18(26):3375–8.
55. DeLeve LD, Valla D-C, Garcia-Tsao G. American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology*. 2009;49(5):1729–64.
56. Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology*. 2010;51(1):210–8.



57. Bach AM, Hann LE, Brown KT, Getrajdman GI, Herman SK, Fong Y, et al. Portal vein evaluation with US: comparison to angiography combined with CT arterial portography. *Radiology*. 1996;201(1):149–54.
58. Parvey HR, Raval B, Sandler CM. Portal vein thrombosis: imaging findings. *AJR Am J Roentgenol*. 1994;162(1):77–81.
59. Tublin ME, Dodd GD, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. *AJR Am J Roentgenol*. 1997;168(3):719–23.
60. Shah TU, Semelka RC, Voultsinos V, Elias J, Altun E, Pamuklar E, et al. Accuracy of magnetic resonance imaging for preoperative detection of portal vein thrombosis in liver transplant candidates. *Liver Transpl*. 2006;12(11):1682–8.
61. Wallner B, Edelman RR, Finn JP, Mattle HP. Bright pleural effusion and ascites on gradient-echo MR images: a potential source of confusion in vascular MR studies. *AJR Am J Roentgenol*. 1990;155(6):1237–40.
62. Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with non-cirrhotic portal hypertension. *Gastroenterology*. 2010;139(4):1238–45.
63. Delgado MG, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol*. 2012;10(7):776–83.
64. Senzolo M, Sartori T, Rossetto V, Burra P, Cillo U, Boccagni P, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int*. 2012;32(6):919–27.
65. Sharma AM, Zhu D, Henry Z. Portal vein thrombosis: when to treat and how? *Vasc Med*. 2016;21(1):61–9.
66. Cui S, Shu R, Yan S, Wu H, Chen Y, Wang L, et al. Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. *Eur J Gastroenterol Hepatol*. 2015;27(8):914–9.
67. Bechmann LP, Sichau M, Wichert M, Gerken G, Kröger K, Hilgard P. Low-molecular-weight heparin in patients with advanced cirrhosis. *Liver Int*. 2011;31(1):75–82.
68. Martinez M, Tandra A, Vuppalaanchi R. Treatment of acute portal vein thrombosis by nontraditional anticoagulation. *Hepatology*. 2014;60(1):425–6.
69. Lenz K, Dieplinger B, Buder R, Piringer P, Rauch M, Voglmayr M. Successful treatment of partial portal vein thrombosis (PVT) with low dose rivaroxaban. *Z Gastroenterol*. 2014;52(10):1175–7.
70. Intagliata NM, Maitland H, Northup PG, Caldwell SH. Treating thrombosis in cirrhosis patients with new oral agents: ready or not? *Hepatology*. 2015;61(2):738–9.
71. Harding DJ, Perera MTPR, Chen F, Olliff S, Tripathi D. Portal vein thrombosis in cirrhosis: controversies and latest developments. *World J Gastroenterol*. 2015;21(22):6769–84.
72. Sogaard KK, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. *BMC Gastroenterol*. 2007;7:34.
73. Hall TC, Garcea G, Metcalfe M, Bilku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. *World J Surg*. 2011;35(11):2510–20.
74. Amitrano L, Guardascione MA, Scaglione M, Pezzullo L, Sangiuliano N, Armellino MF, et al. Prognostic factors in non-cirrhotic patients with splanchnic vein thromboses. *Am J Gastroenterol*. 2007;102(11):2464–70.
75. Chawla YK, Bodh V. Portal vein thrombosis. *J Clin Exp Hepatol*. 2015;5(1):22–40.
76. Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2014;11(7):435–46.
77. Cerini F, Gonzalez JM, Torres F, Puente Á, Casas M, Vinaixa C, et al. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. *Hepatology*. 2015;62(2):575–83.
78. Hollingshead M, Burke CT, Mauro MA, Weeks SM, Dixon RG, Jaques PF. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. *J Vasc Interv Radiol*. 2005;16(5):651–61.
79. Salem R, Vouche M, Baker T, Herrero JJ, Caicedo JC, Fryer J, et al. Pretransplant portal vein recanalization-transjugular intrahepatic portosystemic shunt in patients with complete obliterative portal vein thrombosis. *Transplantation*. 2015;99(11):2347–55.
80. Habib A, Desai K, Hickey R, Thornburg B, Vouche M, Vogelzang RL, et al. Portal vein recanalization-transjugularintrahepatic portosystemic shunt using the transsplenic approach to achieve transplant candidacy in patients with chronic portal vein thrombosis. *J Vasc Interv Radiol*. 2015;26(4):499–506.
81. Qi X, Han G, Yin Z, He C, Wang J, Guo W, et al. Transjugular intrahepatic portosystemic shunt for portal cavernoma with symptomatic portal hypertension in non-cirrhotic patients. *Dig Dis Sci*. 2012;57(4):1072–82.
82. Han G, Qi X, He C, Yin Z, Wang J, Xia J, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with symptomatic portal hypertension in liver cirrhosis. *J Hepatol*. 2011;54(1):78–88.
83. Qi X, Dai J, Jia J, Ren W, Yang M, Li H, et al. Association between portal vein thrombosis and survival of liver transplant recipients: a systematic review and meta-analysis of observational studies. *J Gastrointest Liver Dis*. 2015;24(1):51–9. 4 p following 59.
84. Englesbe MJ, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. *Liver Transpl*. 2010;16(8):999–1005.
85. Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo P, Tector AJ. Portal vein thrombosis is a risk factor for poor early outcomes after liver transplantation: analysis of risk factors and outcomes for portal vein thrombosis in waitlisted patients. *Transplantation*. 2016;100(1):126–33.
86. Sringeri R. Incidental portal vein thrombosis: does it impact the surgical outcomes following liver transplantation? *Liver Transpl*. 2013;19:S289.
87. Hong JJ, Cohn SM, Perez JM, Dolich MO, Brown M, McKenney MG. Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. *Br J Surg*. 2002;89(5):591–6.
88. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Holcomb JB, Ware DN, et al. Secondary abdominal compartment syndrome is an elusive early complication of traumatic shock resuscitation. *Am J Surg*. 2002;184(6):538–43. 544.
89. Cheatham ML, Safcsak K. Is the evolving management of intra-abdominal hypertension and abdominal compartment syndrome improving survival? *Crit Care Med*. 2010;38(2):402–7.
90. An G, West MA. Abdominal compartment syndrome: a concise clinical review. *Crit Care Med*. 2008;36(4):1304–10.
91. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain MLNG, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190–206.
92. Scheppach W. Abdominal compartment syndrome. *Best Pract Res Clin Gastroenterol*. 2009;23(1):25–33.
93. Sugerman HJ. Effects of increased intra-abdominal pressure in severe obesity. *Surg Clin North Am*. 2001;81(5):1063–75. vi.
94. Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. *J Trauma*. 1999;47(6):995–9.

95. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. *J Trauma Acute Care Surg.* 2012;72(4):892–8.
96. Maluso P, Olson J, Sarani B. Abdominal compartment hypertension and abdominal compartment syndrome. *Crit Care Clin.* 2016;32(2):213–22.
97. Sugrue M, Bauman A, Jones F, Bishop G, Flabouris A, Parr M, et al. Clinical examination is an inaccurate predictor of intraabdominal pressure. *World J Surg.* 2002;26(12):1428–31.
98. Kirkpatrick AW, Brenneman FD, McLean RF, Rapanos T, Boulanger BR. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? *Can J Surg.* 2000;43(3):207–11.
99. Iberti TJ, Lieber CE, Benjamin E. Determination of intra-abdominal pressure using a transurethral bladder catheter: clinical validation of the technique. *Anesthesiology.* 1989;70(1):47–50.
100. Fusco MA, Martin RS, Chang MC. Estimation of intra-abdominal pressure by bladder pressure measurement: validity and methodology. *J Trauma.* 2001;50(2):297–302.
101. Corcos AC, Sherman HF. Percutaneous treatment of secondary abdominal compartment syndrome. *J Trauma.* 2001;51(6):1062–4.
102. Savino JA, Cerabona T, Agarwal N, Byrne D. Manipulation of ascitic fluid pressure in cirrhotics to optimize hemodynamic and renal function. *Ann Surg.* 1988;208(4):504–11.



Vijaya Ramalingam, Sikander Ansari,  
and Jonathon Truwit

## Abstract

The association between liver disease and respiratory symptoms is well established. Hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH), and hepatic hydrothorax (HH) are three important pulmonary complications associated with underlying liver disease. Patients with liver disease are also at higher risk of developing ARDS and its associated mortality and morbidity. In this chapter, we review the respiratory complications associated with liver disease.

## Keywords

Hypoxia • Ventilation-perfusion mismatch • Diffusion impairment • Intrapulmonary shunting • Reticuloendothelial system • Vasoactive substances • ARDS • Hepatopulmonary syndrome • Hepatic hydrothorax • Spontaneous bacterial pleuritis • Portopulmonary hypertension • Right heart catheterization • Thoracic compliance • Intra-abdominal pressure • Mechanical ventilation • Liver transplantation

## Learning Objectives Understand

- the mechanisms of hypoxia and respiratory failure
- the pulmonary complications of liver disease and their complications: Acute Respiratory Distress Syndrome (ARDS), hepatopulmonary syndrome, hepatic hydrothorax, portopulmonary hypertension
- the mechanisms in liver disease including effect of ascites, low thoraco-abdominal compliance

V. Ramalingam, M.D.  
Department of Medicine, Medical College of Wisconsin,  
Milwaukee, WI, USA  
e-mail: [vramalingam@mcw.edu](mailto:vramalingam@mcw.edu)

S. Ansari, M.D.  
Department of Medicine, University of Utah School of Medicine,  
Salt Lake City, UT, USA  
e-mail: [Sikandar.Ansari@hci.utah.edu](mailto:Sikandar.Ansari@hci.utah.edu)

J. Truwit, M.D., M.B.A. (✉)  
Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA  
e-mail: [Jonathon.truwit@froedtert.com](mailto:Jonathon.truwit@froedtert.com)

## 11.1 Mechanisms of Hypoxic Respiratory Failure

### Case 1

**A 50-year-old woman with past medical history significant for liver cirrhosis presents to Emergency Department with worsening shortness of breath for 5 days. Vitals: BP 90/60 mmHg, SpO<sub>2</sub> 85% on room air, Pulse 100, temperature 100 F. Patient is visibly tachypneic, dyspneic, and using accessory muscle of respiration. Examination is significant for elevated JVP, ascites and B/L pedal edema.**

- What are the mechanisms of hypoxia in a patient with liver disease?
- Is this patient at increased risk for ARDS and mortality?
- What are the causes of respiratory failure in this patient?

Approximately 10–70% of patients with advanced liver disease may have arterial hypoxia [1–3]. Keys and Snell first

reported the decrease in saturation of arterial blood for oxygen in patients with liver cirrhosis. They later explained this phenomenon due to decreased oxygen affinity of hemoglobin due to increased 2,3-diphosphoglycerate (DPG) in erythrocytes [4, 5]. When measurement of partial pressure of oxygen ( $\text{PaO}_2$ ) became technically possible, it was shown that  $\text{PaO}_2$  was also lower in these patients indicating defective gas exchange mechanism. Three components of gas exchange abnormalities result in hypoxia in patients with liver disease: intrapulmonary shunting, diffusion impairment, ventilation-perfusion mismatch. It is well known that patients with cirrhosis generally hyperventilate and hence hypoventilation can be ruled out as a cause of hypoxia in these patients [6, 7].

Rodman and associates first described ventilation-perfusion (V/Q) mismatch as a cause of hypoxia in patients with advanced liver disease. Gas exchange is optimal when ventilation and perfusion are well matched. That is, when the V/Q ratio is approximately 1 [8]. A disproportionate change in either ventilation or perfusion would cause hypoxia. The major defect that underlies V/Q mismatch is intrapulmonary vascular dilatation or abnormal dilatation of pulmonary vascular bed at precapillary level resulting in a disproportionate increase in perfusion relative to alveolar ventilation associated with an elongated path for oxygen to reach the central blood flowing in the pulmonary vessels (see below). Patients with advanced liver disease also have decrease in hypoxic pulmonary vasoconstriction. Under normal physiological circumstances, alveolar hypoxia results in constriction of pulmonary vessels that supply hypoxic units and this maintains the V/Q ratio by reducing the perfusion in areas of low ventilation. In patients with advanced liver disease, hypoxic pulmonary vasoconstriction is reduced or lost. However, hypoxic pulmonary vasoconstriction is not uniformly affected in all patients.

Intrapulmonary shunting was first described by Hoffbauer and Rydell in 1956 [9]. It refers to the entry of systemic venous blood into the arterial circulation without exposure to gas exchange. There are three mechanisms of shunting: (1) Physiologic shunting in which venous blood flows through non-ventilated alveoli. Interstitial edema due to volume overload, atelectasis due to elevated hemi diaphragms from tense ascites and/or pleural effusions are typical examples. (2) Anatomic communications between pulmonary arteries and veins and thus bypassing the capillary-alveoli interfaces, and (3) dilated capillary and precapillary beds in which diffused oxygen ineffectively reaches the midstream deoxygenated hemoglobin molecules. Shunt may be normal or abnormally increased in patients with advanced liver disease [10, 11]. In 1961, Abelman et al. showed that patients with cirrhosis had venous admixture of 8% to 20% of total blood flow, above the normal maximum of 7% in all patients [12]. Another study by Williams et al. demonstrated an average

venous admixture of 9.7% in cirrhotic patients [13]. This increase in venous admixture is due to true anatomic extra-cardiac right-to-left shunts attributed to pulmonary AV malformations [6]. However, this is not a frequent finding and evidence of such AV communication was demonstrated in only 1 of 14 postmortem studies [14]. Another possibility of anatomic shunting is the presence of abnormal communication between portal and pulmonary venous systems. However, these channels are unlikely to cause hypoxia due to smaller flow through these channels and higher oxygen content of portal venous blood [14, 15]. It should be noted, that the presence of abnormal liver function tests, ascites, splenomegaly, portal or pulmonary hypertension, or digital clubbing are not predictive of intrapulmonary shunting (Table 11.1) [16].

Premature closure of airways causing VQ mismatch is another cause of hypoxia in patients with liver disease [16]. In a study of 10 cirrhotic patients, the closing lung capacity was higher than normal, and in eight patients it was greater than the functional residual capacity, indicating the presence of airway closure and gas trapping during resting tidal volume breathing. Both at residual volume and at functional residual capacity, gas trapping in the lower lung zones was increased [17, 18]. In liver cirrhosis, decreased ventilation from airway closure affects the ventilation-perfusion ratio of the dependent lung zones. It is suggested that the premature

**Table 11.1** Mechanisms of arterial hypoxemia in patients with hepatopulmonary syndrome

Mechanism	Causes	Role of supplemental oxygen
V/Q mismatch	<ul style="list-style-type: none"> <li>• Perfusion of poorly ventilated alveoli e.g.—interstitial edema, atelectasis</li> <li>• Increased perfusion due to abnormal dilatation and increase in number of pulmonary capillary and precapillary vessels</li> <li>• Impaired hypoxic pulmonary vasoconstriction</li> <li>• Premature closure of airways</li> </ul>	Arterial hypoxia is usually reversible
Shunting	<ul style="list-style-type: none"> <li>• Intrapulmonary shunting</li> <li>• Porto pulmonary shunting</li> <li>• Pleural shunting</li> </ul>	Shunts should not respond significantly to 100% supplemental oxygen
Diffusion impairment	<ul style="list-style-type: none"> <li>• Diffusion-perfusion mismatch</li> </ul>	Supplemental oxygen may increase the driving pressure of alveolar oxygen and thus may increase oxygen diffusion to improve hemoglobin saturation

airway closure may be due to mechanical compression of small airways by dilated blood vessels and/or interstitial pulmonary edema [16–18].

Diffusion impairment is another important cause of hypoxia. Due to marked dilatation of precapillary and capillary beds, diffused oxygen ineffectively reaches the mid-stream deoxygenated hemoglobin molecules. This is further aggravated by high cardiac output secondary to intrapulmonary shunting [6]. Shunts should not respond significantly to 100% supplemental oxygen. However, supplemental oxygen may increase the driving pressure of alveolar oxygen and thus may increase oxygen diffusion to improve hemoglobin saturation.

### 11.1.1 Role of Liver in Protecting Lungs

Patients with the adult respiratory distress syndrome and multiple organ system failure have a high mortality rate. Among extrapulmonary organs, the liver plays a central role in regulating cytokine kinetics relevant to acute lung injury [19]. The hepatic reticuloendothelial system (RES) clears vasoactive substances implicated in the development of acute lung injury [20]. Hepatocytes and Kupfer cells uptake and detoxification of gut derived and blood-borne bacteria, endotoxin, activated coagulation factors and endogenous proinflammatory mediators is also critical in systemic host defense [21, 22]. In patients with hepatic dysfunction, this filtering ability of liver is compromised resulting in systemic overflow of inflammatory mediators [22, 23]. Nakao et al. demonstrated that intravenous injection of endotoxin in rats with drug induced liver failure resulted in significantly higher levels of blood endotoxin compared to rats with normal liver function despite normal blood endotoxin concentrations in both groups of rats before inducing liver failure [24]. Liver failure results in reduced inactivation of endotoxin in plasma and also impaired hepatic clearance.

In a rat model of biliary obstruction, authors demonstrated impaired hepatic RES bacterial clearance and increased pulmonary localization of viable organisms [25]. High plasma endotoxin levels before liver transplantation and at the end of the anhepatic phase was associated with graft failure and a high mortality [26]. In a study of patients receiving liver transplantation, a strong correlation was also observed between endotoxemia and the need for ventilator dependency postoperatively [27].

Severe hepatic dysfunction not only predisposes patients to ARDS but also significantly modulates its resolution. Besides being at increased risk of developing ARDS, patients with chronic liver disease are also at higher risk of developing severe ARDS and associated morbidity and mortality [28]. Chronic alcohol abuse also depletes the glutathione (GSH) stores in lungs. GSH protects the lung from

oxidative injury and its depletion in the lung increases the risk of oxidative damage due to inability to scavenge oxygen free radicals [29–31]. Both humoral and cellular immunity are impaired in patients with end-stage liver disease (ESLD) thus increasing the risk of infection including respiratory tract infection. Diffuse fibrosis of hepatocytes results in defective opsonization due to decreased synthesis of C3 complement [32]. Impaired antibacterial activity of alveolar macrophages results in increased risk of respiratory tract infections [33]. Alveolar macrophages exposed to microorganisms produce the cytokines tumor necrosis factor-alpha, interleukin (IL)-1 beta, and IL-6 that are important to lung defense. This is also impaired in patients with ESLD [34].

### 11.1.2 ARDS and Liver Disease

Several studies have shown a higher incidence of ARDS in patients with underlying liver disease. Prior to low tidal volume ventilation era, ARDS in patients with liver failure had a mortality of nearly 100% outside the transplant setting [35–38]. However, there has been a decline in overall mortality rate for patients with ESLD admitted to ICU and it ranges from 35% to 70% [39–43].

Using data from National Mortality Followback Study, Tenhoo et al. showed the positive association between ARDS mortality and the presence of sepsis and cirrhosis. Compared to patients without sepsis and cirrhosis, patients with these conditions were more likely to die from ARDS [44]. In a retrospective study of 29 patients with end-stage liver disease compared to 44 intensive care patients without ESLD, ARDS occurred in 23 of 29 patients (79%) with ESLD versus 3 of 44 patients (6.8%) without ESLD. Regardless of etiology and ventilatory support, ARDS was uniformly irreversible in all 23 ESLD patients. They also reported 93% mortality in 29 patients with end-stage liver disease who developed ARDS while waiting for liver transplantation.

A prospective multicenter study by Doyle et al. showed that underlying chronic liver disease was the second most significant adverse prognostic factor for survival in patients with acute lung injury. In their study, mortality from ALI in patients with chronic liver disease was higher (77%) compared to ALI in patients without a diagnosis of chronic liver disease [28]. Montgomery and colleagues found that severe hepatic dysfunction appeared to be an indirect cause of death in patients with ARDS [37]. In a retrospective study of 24 patients with ARDS, Schwartz and coworkers found that acute liver dysfunction was associated with increased mortality [45]. Another study also found that underlying liver cirrhosis was independently associated with a very poor outcome in patients with ARDS [46].

## 11.2 Cause of Respiratory Failure: Hepatopulmonary Syndrome

### 11.2.1 Definition and Epidemiology

The term Hepatopulmonary syndrome (HPS) was coined by Kennedy and Knudson in 1977. It is characterized by the triad of impaired oxygenation, underlying liver disease and intravascular pulmonary vasodilatation (IPVD) (Table 11.2) [47, 48]. The prevalence of HPS ranges from 5% to 32% [49]. However, there are no prospective multicenter prevalence studies to date. HPS affects patients of all ages and is more common in whites than in Hispanics and African Americans [50].

### 11.2.2 Pathophysiology

The hallmark of HPS is increase in the number of pulmonary precapillary and capillary vessels and increase in the diameter from a normal range of <8–15  $\mu\text{m}$  to 15–100  $\mu\text{m}$  [15, 48]. In addition, pleural and pulmonary arteriovenous malformations and portopulmonary venous anastomoses may also be seen although less common [15, 48]. The rapid or direct passage of mixed venous blood through these abnormal communications into the pulmonary veins leads to impaired oxygenation. The abnormal dilatation also results in true intrapulmonary vascular shunting, resulting in right-to-left shunts and diffusion-perfusion defect (described above). These abnormal communications which worsen VQ mismatch and shunt predominate in lung bases. This feature, coupled with impaired pulmonary vasoconstriction to hypoxia leading to a relatively fixed pulmonary vascular tone unable to respond to gravitational changes, explains platypnea (dyspnea on standing) and orthodeoxia (fall in  $\text{PaO}_2$  by 5% or more or by 4 mmHg or more on standing).

Multiple mechanisms have been proposed to explain IPVD. Increased pulmonary production of nitric oxide plays an important role [51]. Animal studies have shown increased activity of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) in the pulmonary microcirculation [52]. Consistent with pulmonary

overproduction in HPS, nitric oxide levels are increased in exhaled air and normalize after liver transplantation [51]. Nitric oxide production also seems to be increased by endothelin (ET)-1 mediated activation of eNOS. In HPS, there is increased hepatic production of ET-1 and increased expression of ET-B receptors in pulmonary vasculature [53, 54]. Bacterial translocation and endotoxemia also seem to play an important role in NO overproduction by causing pulmonary accumulation of macrophages, which express iNOS [55, 56]. Experimental studies have also demonstrated a role for TNF-alpha in the genesis of HPS. In animal studies, pentoxifylline prevented development of hyperdynamic circulatory state and hepatopulmonary syndrome, probably by inhibiting the effects of tumor necrosis factor-alpha on vascular nitric oxide synthase and intravascular macrophages [57, 58]. NO-mediated increased expression of heme oxygenase-1 and carbon monoxide production, worsening the impaired pulmonary vasoconstriction, has also been described in HPS [59, 60]. In experimental models of HPS, an increase in pulmonary angiogenesis accompanied by activation of VEGF-A-associated angiogenic pathways has been described. Pentoxifylline was shown to downregulate VEGF-A mediated pathways and decrease the angiogenesis (Box 11.1) [61].

#### 11.2.2.1 Clinical Manifestations

There are no specific symptoms or signs for HPS. Dyspnea on exertion or at rest is the most common symptom and it usually presents after years of having liver disease. Platypnea and orthodeoxia are seen in about 25% of patients with HPS. The presence of spider nevi, cyanosis, digital clubbing, and severe hypoxia ( $\text{PaO}_2 < 60$  mmHg) strongly suggests HPS.

Patients with HPS may have marked hypoxia during sleep despite the presence of only mild to moderate daytime hypoxia. Chest radiographs may be normal or may show bibasilar nodular or reticulonodular opacities to reflect pulmonary vascular abnormalities. The only pulmonary function test that is consistently reduced is diffusion capacity for carbon monoxide. However, this is not specific and may not normalize after liver transplantation (LT). HPS is classified based on A-a gradient and  $\text{PaO}_2$  (Table 11.3).

**Table 11.2** Triad of HPS

Clinical feature	Definition
Impaired oxygenation	A-a gradient $\geq 15$ mmHg or $\text{PaO}_2 < 80$ mmHg on room air
Liver disease	Portal hypertension with or without cirrhosis
Abnormal pulmonary vascular dilatation	Positive findings on contrast-enhanced transthoracic echocardiography or abnormal uptake in the brain (>6%) with lung perfusion scan

**Table 11.3** Classification of HPS

Severity	Room air $\text{PaO}_2$ (mm Hg) with an A-a gradient $\geq 15$ mmHg
Mild	$\geq 80$
Moderate	$\geq 60$ to $< 80$
Severe	$\geq 50$ to $< 60$
Very Severe	$< 50$
	$< 300$ on 100% oxygen



### 11.2.2.2 Diagnosing HPS

Diagnosis of HPS requires demonstration of impaired arterial gas exchange and pulmonary vascular dilatation in the setting of underlying liver disease. Portal hypertension is not a prerequisite for diagnosis of HPS as impaired oxygenation due to pulmonary vascular dilatation can be seen in any acute or chronic liver disease. In patients with underlying lung disease, additional tests may be required to attribute the degree of hypoxia to HPS.

Contrast-enhanced transthoracic echocardiogram (CTTE) is the most sensitive test to detect IPVD. It is performed by injecting agitated saline intravenously during routine transthoracic echocardiography. The microbubbles are usually absorbed in the alveoli and they do not pass through normal capillary diameter. In the presence of IPVD, these bubbles pass through abnormally dilated pulmonary vasculature and appear in the left atrium 3–6 cardiac cycles after injection. Although contrast-enhanced transesophageal echocardiography may increase the sensitivity of detecting IPVD by directly detecting microbubbles emanating from the pulmonary veins, it is more invasive and expensive and is not routinely needed.

Another method to demonstrate shunting is radionuclide lung perfusion scan with technetium-labeled macroaggregated albumin (MAA) particles in which particles measuring 20–50  $\mu\text{m}$  in size are injected intravenously. They are caught in the pulmonary microvasculature of healthy individuals. In patients with HPS, they shunt through the abnormal pulmonary vascular dilatation and are distributed in brain, kidneys, and spleen. Based on the quantitative distribution of these particles in the brain and lungs, degree of shunting can be calculated. Although the MAA scan is less sensitive than CTTE as it cannot distinguish between intracardiac and intrapulmonary shunting, it is helpful in assessing the contribution of HPS to hypoxia in patients with intrinsic lung disease with severe hypoxia ( $\text{PaO}_2 < 60 \text{ mmHg}$ ) [62]. An MAA shunt greater than 6% points to HPS as the major contributor to hypoxia. Another advantage of MAA scan is its utility in stratifying patients for postoperative mortality following LT. A large MAA shunt ( $>20\%$ ) detected in patients with very severe HPS has been associated with high mortality after LT [63].

Angiography is a more invasive test for the detection of IPVD, but is not clinically useful for diagnosing HPS. It may be considered to evaluate for percutaneous embolization of pulmonary arteriovenous malformations in the setting of severe hypoxia ( $\text{PaO}_2$  is  $<60 \text{ mmHg}$ ) [64].

### 11.2.3 Treatment

The only effective treatment is liver transplantation (OLTx) which can result in resolution of HPS or improvement in

gas exchange. The 5-year survival rate of patients with HPS without OLTx is 23% compared to 76% post OLTx [65]. Pretransplantation  $\text{PaO}_2$  of less than 50 mmHg alone or in combination with a greater than 20% MAA shunt fraction is associated with 7.5-fold increase in posttransplantation mortality rate compared to patients with less severe HPS [66–68]. Hence patients with  $\text{PaO}_2 < 50 \text{ mmHg}$  should be carefully considered for transplantation while  $\text{PaO}_2$  of 50–60 mmHg is a firm indication for transplantation [48, 69].

## 11.3 Hepatic Hydrothorax

### Case 2

**A 62-year gentleman with PMH significant for cirrhosis and portal hypertension is admitted with fever and abdominal pain for 2 days. Examination is significant for decreased breath sounds on right side and ascites. A bedside ultrasound of chest revealed a ~ 1000 mL right sided pleural effusion.**

- What is the most common cause of pleural effusion in patients with cirrhosis?
- What are the diagnostic criteria for hepatic hydrothorax?
- Does this patient need a diagnostic thoracentesis to rule out infection despite a negative paracentesis?

Hepatic hydrothorax (HH) is a transudative pleural effusion, usually greater than 500 mL, seen in patients with portal hypertension in the absence of underlying pulmonary, cardiac or pleural diseases.

### 11.3.1 Pathophysiology

The key mechanism of hepatic hydrothorax is the passage of ascitic fluid from peritoneal cavity to pleural space through small diaphragmatic defects called pleuroperitoneal communications. These communications, usually  $<1 \text{ cm}$  in size, are predominantly seen on the right hemidiaphragm and is attributed to the right hemidiaphragm being more tendinous and less muscular than the left hemidiaphragm [70]. The right side is more tendinous because of the close anatomic relationship of the bare areas of the liver with the diaphragm [71–73]. This may explain the predominance of hepatic hydrothoraces on the right side. Due to poorly understood reasons, up to 20% of the population may have these defects. In patients with liver disease, the raised abdominal pressure secondary to ascites and the diaphragmatic thinning caused by malnutrition may also increase the gaps between diaphragmatic muscle fibers. The negative intrathoracic pres-



sure during inspiration also contributes to the one-way flow of fluid from peritoneal cavity to the pleural space.

### 11.3.2 Clinical Manifestations and Diagnosis

Hepatic hydrothorax, the most common cause of pleural effusions in cirrhosis, is seen in approximately 5% to 10% of patients with cirrhosis [74, 75]. The presenting symptoms could be cough, dyspnea, chest discomfort depending on the amount of pleural effusion, rapidity of accumulation, and underlying pulmonary reserve. Chest x-rays reveal that HH is right-sided in 70% of cases, left-sided in 18%, and bilateral in 12% [75]. It should always be suspected in a patient with liver disease and pleural effusion, typically right-sided effusion. Ascites is not required for diagnosis and up to 20% of patients with HH may not have clinically significant ascites. Even in the absence of ascites, pleuroperitoneal communications can be demonstrated by the intraabdominal administration of 99mTc-human albumin or 99mTc-sulphur colloid and its detection in the pleural space [76, 77]. However, this is rarely used in the clinical setting. Chest radiography is used to detect the pleural effusion. Thoracentesis is required to identify the cause of pleural fluid accumulation, detect any infection and to provide symptomatic relief. The characteristic features of HH are listed in Box 11.2 [69, 73, 78, 79].

### 11.3.3 Treatment

The development of HH is a complication of advanced liver disease and patients with HH should be evaluated for liver transplantation. Dietary sodium restriction and diuretic agents are the first line treatment of HH. Fluid mobilization from the pleural cavity may be slower than from the peritoneal cavity resulting in refractory HH in about 20% of patients [80].

Therapeutic thoracentesis is indicated in patients with symptomatic HH, and refractory HH. However, it is associated with increased risk of bleeding, infection, and protein loss. There is no data-supported limit to volume of fluid removal [81]. It has been shown that re-expansion pulmonary edema is rare and independent of the amount of fluid removed. Large effusions can be drained safely in the absence of chest discomfort or if end-expiratory pleural pressure remains below—20 cm H<sub>2</sub>O [82]. Alternative treatments should be considered if a patient requires therapeutic thoracentesis once every 2–3 weeks despite optimum medical management. Chest tube placement is associated with increased risk of fluid depletion, protein loss, infection, poor wound healing, fluid depletion, and renal failure. Hence it should be avoided in the absence of empyema [83–85].

Transjugular intrahepatic portosystemic shunt (TIPS) is the standard of care treatment for refractory hydrothorax with response rates of 70%–80% [80, 86]. Contraindications to TIPS in HH include hepatic encephalopathy, severe liver dysfunction, right heart failure, pulmonary hypertension, and complete portal vein thrombosis. Patients aged >60, with an elevated baseline creatinine, a MELD score >15, a Child Pugh score >10, and a poor response to TIPS have an increased mortality following TIPS [80, 87, 88].

Video assisted thoracoscopic surgery with pleurodesis is reserved for patients with poor response to medical therapy and have either failed TIPS or are poor candidates for TIPS.

However, due to rapid reaccumulation of pleural fluid, pleurodesis is considered inferior to transjugular intrahepatic portosystemic shunt. Also, complications such as pleurocutaneous fistula, empyema, and death have been reported following VATS. Hence, VATS with pleurodesis is reserved as a palliative treatment.

There is a renewed interest about placement of a pleurovenous or peritoneovenous shunt in selected patients with refractory ascites. Harry H. LeVeen et al. introduced the method of performing continuous abdominal paracentesis called peritoneovenous shunting [89]. It involves recirculating the protein-rich ascitic fluid back into the central circulation through a subcutaneous plastic cannula with a one-way pressure valve. In 1970, Kirsch et al. introduced the Denver shunt for peritoneovenous shunting in patients with abdominal and pleural cirrhotic ascites and is currently being used to treat both cirrhotic and malignant pleural effusions and peritoneal ascites [90]. When the pressure gradient between the peritoneal or pleural space and the venous system falls below 3–5 cm H<sub>2</sub>O, the valves close and when the pressure gradient increases above 5 cm H<sub>2</sub>O, they open to facilitate continuous flow of fluid. The use of the Denver shunt has been limited by adverse events like shunt occlusion, ascitic fluid leak and infection, bleeding, pneumothorax, and pneumoperitoneum [91].

## 11.4 Spontaneous Bacterial Pleuritis

Spontaneous bacterial pleuritis (SBPL) or spontaneous bacterial empyema is an underdiagnosed pleural complication of cirrhosis. It is defined as spontaneous infection of hepatic hydrothorax in the absence of pneumonia.

### 11.4.1 Pathophysiology

Two mechanisms have been postulated to explain SBPL: (1) Translocation of infected peritoneal fluid to the pleural space via diaphragmatic defects. However, SBP is not a prerequi-

site for the diagnosis of SBPL as cases of SBPL have been reported in the absence of SBP. (2) Translocation of enteric microorganisms to the pleural space due to spontaneous bacteremia [72, 92, 93].

#### 11.4.2 Clinical Manifestation and Diagnosis

The incidence ranges from 10% to 16% in cirrhotic patients with HH [92, 93]. A high level of suspicion is required to diagnose SBPL because patients may not always have fever, pleuritic chest pain and can present with worsening mental status, or renal function. Risk factors for developing SBPL include advanced liver disease, higher Child-Pugh score, low pleural fluid total protein ( $<1$  mg/dL), and C3 levels [94]. The microorganisms most commonly involved are similar to SBP and include Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*), *Streptococcus* species, and *Enterococcus* species. Nearly 40% of patients who develop SBPL do not have concomitant spontaneous bacterial peritonitis (SBP) and hence it is important to perform thoracentesis in patients with suspected infection and negative paracentesis [83].

The diagnosis needs a positive pleural fluid culture and a polymorphonuclear cell greater than.

250 cells/mm<sup>3</sup> or a negative pleural fluid culture and a polymorphonuclear cell greater.

than 500 cells/mm<sup>3</sup> in the absence of pneumonia or contiguous infection on chest imaging. The presence of pus in the pleural space is not required for diagnosis of SBPL [93, 94].

#### 11.4.3 Treatment

Antibiotic therapy is similar to management of SBP with a third-generation cephalosporin. Prophylactic antibiotic therapy should be initiated after an episode of SBPL. SBPL is associated with a mortality of 20% [69]. Chest tube placement is contraindicated in the absence of empyema.

### 11.5 Mechanisms in Liver Disease Including Effect of Ascites, Low Thoraco-abdominal Compliance

#### Case 3

**A 70 year old patient who has diagnosed cirrhosis of the liver from Hepatitis C, and previously needed weekly therapeutic paracentesis, comes to the emergency room with a distended abdomen which is tense to palpation, no fevers or chills. He has mild hepatic encephalopathy, dyspnea at rest, is using his accessory muscles of respiration.**

**Has low blood pressure and tachycardia and on further evaluation had kidney injury.**

- **How is his increased abdominal pressure due to tense ascites, causing multi-organ failure?**

The abdominal and thoracic compartments are connected to each other by anatomy and thus also physiology. In a clinical setting the thoracic compliance, consisting of the thoracic wall and the lungs are easy to interpret, but at times the abdominal compliance is overlooked. Understanding how intra-abdominal pressure affects abdominal visceral function and pulmonary mechanics is important for intensivists taking care of advanced liver disease patients in the ICU.

In liver disease patients, ascites is often present increasing intra-abdominal volume and intra-abdominal pressure [95]. This increase in pressure causes outward forces on the abdominal wall including the anterior abdominal wall, the diaphragm, and also compressive forces on the organs inside the abdominal cavity. The hollow organs, such as, the large and small intestine are able to absorb some of this pressure as they are filled with gas, and thus are more compressible when compared to the solid organs and blood vessels.

Accumulation of ascites in these patients is generally a gradual process, thus volume accumulated with milder increases in intra-abdominal pressure (IAP). However, when the volume exceeds the abdomen's capacity to accommodate from either too much volume or a rapid accumulation, patients can develop tense ascites with an IAP significant enough to lead to abdominal compartment syndrome. In this scenario, increased IAP can compress the hollow organs and the intestinal blood supply. An IAP above 20 mmHg can decrease perfusion of the gut and increase chances of ischemic damage and translocation of bacteria [96–98]. Persistent increase in IAP can also decrease liver perfusion and thus liver function and also increase pressure in esophageal varices, if present, increasing chances of variceal bleeding [99]. Increased IAP can also decrease renal perfusion causing kidney injury, in the patient's whose kidneys are already at risk due to hepatorenal syndrome.

Increased IAP also affects the diaphragm and in return transmits pressures to the thoracic compartment [100]. Around 50% of the IAP is transmitted across the diaphragm, increasing the intra-thoracic pressure [101] as the IAV pushes the diaphragm upwards, the lungs cannot expand as they usually would and the tidal volume decreases, and if the patient would need increased ventilation, the accessory muscles of respiration would be activated earlier than in a patient who didn't have ascites. Compressive atelectasis and decreased tidal volumes can lead to hypercapnia and hypoxia. When these patients are on invasive mechanical ventilation due to the IAP transmitted to the thoracic cavity they have higher peak and plateau pressures. These increased

pressures can be challenging to set ventilator a mode to, to keep up with ventilation and oxygenation, particularly if this increase in pressures is mistaken for signs of ARDS. If mistaken for ARDS when it is not present, this may lead to high PEEP strategies, which may prevent ARDS, but the higher PEEP may in return increase the IAP, as intra thoracic pressure rises are also transmitted to the abdominal compartment [102].

When providing respiratory support, NIPPV should be used in a closely monitored setting, keeping in mind that liver disease patients are prone to developing encephalopathy when critically ill and once indicated, intubation and mechanical ventilation should not be delayed. At this time there are no guidelines as to which ventilator modes are better for liver disease patients with increased IAP, but attention should be given to keeping plateau pressures, in a range, which will not drastically increase intra-abdominal pressures, while reaching adequate ventilation and oxygenation.

In extreme cases the IVC can be partially compressed causes decreased systemic venous return and thus decreased RV output. When compounded with high pulmonary artery pressures in the case of porto-pulmonary hypertension the cardiac output can significantly reduce [101, 103]. In the most severe cases of increased IAP, the intra thoracic pressure may raise enough to impede cranial venous drainage via the internal jugular veins. In patients with increased intracranial pressure due to cerebral edema, as seen with severe hepatic encephalopathy, this reduced drainage may be detrimental to the patient [104].

Most surgical methods of measuring intra-abdominal pressures are limited to research and the clinically accepted gold standard is measurement of bladder pressure. A normal bladder pressure is 0–5 mmHg, and in critically ill patients a bladder pressure is 5–7 mmHg is common [105]. When the bladder pressure increases above 12 mmHg, the pathologic effects of IAP, can be seen. One must keep in mind that IAP due to ascites is a gradual process, and thus the complications mentioned above are present in the more advanced cases, when compared to other causes like pancreatitis or abdominal trauma, in which IAP rises quickly [106].

In ascites the increased IAP due to increased intra-abdominal volume from the ascites fluid. There seems to be a linear relationship with the ascites volume and IAP as long as the abdominal wall compliance remains the same. Paracentesis to remove large volumes decreases IAP and also can show immediate improvement in dyspnea and lung mechanics [107]. Large volume paracentesis should be targeted keeping in mind the risk of hemodynamic compromise and replacing intravascular volume with albumin as indicated.

Other more basic strategies which could be used are nasogastric stomach decompression, and to avoid large volume resuscitations to control the rise in IAP. Keeping the head of

the bed at 30 degrees is standard practice and a higher angle such as 45 degrees may compress the abdominal cavity increasing the IAP [108]. Prone positioning, compressive abdominal dressings should be avoided as they reduce abdominal compliance. Sedation and when needed neuromuscular blockers can be used if the patient's respiratory efforts, and patient-ventilator desynchrony are contributing to the increased IAP [109].

### 11.5.1 Mechanical Ventilation in Liver Disease

As acute liver failure or chronic liver disease patient's get admitted to the ICU many undergo respiratory failure. Many need intubation and mechanical ventilation for airway protection due to encephalopathy, in this setting up adequate ventilation strategies does not seem to be a challenge. Liver disease patients who undergo intubation and mechanical ventilation have a high one year mortality, reaching up to more than 80% according to some reports [110, 111]. It is the patients who need mechanical ventilation due to ARDS, pneumonias, volume overload or transfusion reactions, which are more difficult to oxygenate and ventilate.

The intensivist has many modes to use at his or her disposal, including the conventional AC volume control or pressure control modes and many others including the APRV and proportional assist modes. Most of the trials done in the past excluded advanced liver disease patients thus there is a paucity of data specific to the liver disease patients. There is no data to help mechanical ventilation strategies for hepato-pulmonary syndrome or for porto-pulmonary hypertension.

Extrapolating from the data available for the general adult population, in patients with ARDS and liver disease, low tidal volumes below 6 ml/kg should be used to prevent volutrauma, along with a cautious increase in PEEP to minimize alveolar collapse but at the same time being mindful it may increase intra-abdominal pressure [112, 113]. In this patient population where liver disease is associated with metabolic acidosis from kidney injury and lactic acidosis, permissive hypercapnea may be a challenge while keeping the PH in an acceptable range [114].

Patients with liver disease, when in a compensated state, function at higher respiratory rate and minute ventilation, resulting chronic respiratory alkalosis [48]. Tidal breathing may be compromised when large pleural effusions are present and restricting lung expansion. This may result in respiratory failure or difficulty in mechanical ventilation. In these cases, therapeutic thoracentesis should be considered. At times when intra-abdominal pressure is increased and leading to respiratory failure, measures should be used to decrease IAV and thus IAP, including therapeutic paracentesis.

Just like in any other intubated patient, sedation should be tailored to the patient's needs. Altered pharmacokinetics and pharmacodynamics should be taken into account in liver disease patients, when choosing analgesic and sedative agents, to avoid over sedation and prolonged intubation and thus reducing overuse of resources and ventilator associated pneumonias [115–118]. Further studies are needed to formulate an optimal approach to mechanical ventilation in the liver disease patients.

NIPPV has been studied in patients with COPD and CHF, but not specifically in liver disease patients. It can be used in in post liver transplant patients with mild respiratory failure with CHF or COPD, [119, 120] but alerted mental status is always a concern in advanced liver disease. If used NIPPV should be used with caution and intubation and mechanical ventilation should not be delayed, if it is indicated.

## 11.6 Portopulmonary Hypertension

### Case 4

**A 45 year old male with a history of autoimmune hepatitis related cirrhosis complains of dyspnea and lightheadedness at rest. Since he was diagnosed with cirrhosis he has been compliant with his medications and also his diuretics and never needed paracentesis. Now he gets short of breath after walking across the hall, and his wife says his face becomes pale when he exerts himself. He also has developed pedal edema. He has no wheezing and no coughing but sometimes gets dull achy chest pain on exertion. His chest X-ray reveals large pulmonary vessels without pulmonary edema. He was about to get referred to the liver transplant clinic after his last visit with his general Hematologist.**

- **What could be the etiology of his dyspnea, and what work up should be initiated? How may this change his chances of getting a liver transplant?**

Portopulmonary hypertension (POPH) was first described by Mantz and Craige in 1951 [121]. Autopsy revealed intimal thickening of medium and large pulmonary arteries and endothelial proliferation of terminal pulmonary arterioles. POPH is defined as elevation of pulmonary artery pressure due to increased pulmonary vascular resistance in the setting of portal hypertension. It is hemodynamically described as mean pulmonary artery pressure of  $>25$  mmHg, pulmonary artery occlusion pressure of  $<15$  mmHg, and pulmonary vascular resistance of  $>240$  dyn/s/cm<sup>-5</sup>. While the patient must have portal hypertension, he/she may or may not have advanced liver disease. POPH is included in group I of the 2013 Nice classification of pulmonary hypertension [122].

### 11.6.1 Epidemiology

When evaluating dyspnea or signs of heart failure in a patient with portal hypertension pulmonary hypertension should be considered. A large autopsy study showed that pulmonary hypertension (PH) was 5 times more likely in cirrhotic patients than those without liver disease. PH occurred with a prevalence of 0.13% in all patients, but with a prevalence of 0.73% among patients with cirrhosis [123]. In a study of 1235 patients, 66 patients (5.3%) were found to have POPH [124]. In a prospective hemodynamic study of 507 patients with portal hypertension, 2% were found to have POPH [125]. In another prospective study of 165 patients, POPH was diagnosed in 10 patients (6.1%) [126]. POPH was diagnosed in 5.3% of the cases (174 of 3525) in The Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL registry) [127]. In a retrospective analysis of all patients referred to a French Referral Center for pulmonary arterial hypertension with the diagnosis of PoPH between 1984 and 2004, 154 patients (10.4%) were diagnosed with POPH [128].

### 11.6.2 Clinical Manifestations

The symptoms and signs of POPH are similar to those in other types of pulmonary arterial hypertension and depend on the severity of right ventricular failure. Dyspnea on exertion is the most common presenting symptom in more than 80% of patients [129]. As the disease progresses, patients can present with fatigue, chest pain due to right ventricular ischemia, and dyspnea at rest. POPH, like PH, when mild may be elusive to prompt diagnosis and can be mistaken for other processes. Mild POPH may also be difficult to diagnose unless there is a high suspicion in this particular patient population. A loud pulmonary component of the second heart sound, a left parasternal heave, jugular venous distention, along with other signs of right heart failure may be noticed as the disease progresses [130, 131].

### 11.6.3 Pathogenesis

The exact etiology of POPH is unclear and remains to be determined. Several processes have been proposed and it is possible that the etiology is multifactorial. Persistent high vascular pressures with vascular endothelial stress has been proposed as an etiology. The systemic vascular resistance is low and to maintain adequate perfusion the cardiac output is increased this causing more blood flow through the pulmonary vasculature [132–135]. This added stress causes damage to the vascular wall and may cause changes seen in POPH.



Increased splanchnic blood flow and porto-systemic shunts may result in exposing the pulmonary system to blood that has bypassed the liver and its metabolic functions. This exposes the lungs to substances like ET-1, Interleukin 1 and 6, VIP, Glucagon, serotonin [136], thromboxane 21 and various other substances and toxins for the GI flora. Liver specimens obtained from 62 cirrhotic patients at the time of liver transplantation showed higher levels of ET-1 compared to controls. ET-1, a potent systemic and pulmonary vasoconstrictor also aggravates portal hypertension by increasing the hepatic stellate cell contraction and sinusoidal tone. Studies have shown elevated systemic and splanchnic ET-1 levels in patients with cirrhosis and POPH compared to cirrhotic patients without POPH. Prostacyclin, a potent vasodilator and inhibitor of platelet adhesion and cell growth, and is also decreased in patients with POPH due to deficiency of endothelial prostacyclin synthase in lung parenchyma. The role of ET-1 and prostacyclin in POPH is also supported by the therapeutic role of ET-1 antagonists and prostacyclin analogues in POPH. These factors, and possibly other yet undiscovered mechanisms cause characteristic pulmonary vascular pathology indistinguishable from other phenotypes of PAH [137, 138].

#### 11.6.4 Diagnosis

Transthoracic echocardiography remains as a good start of a work up for suspected POPH, as in other forms of PAH, a right ventricular systolic pressure above 30–50 mmHg is concerning for PH. With structural signs of RV pressure overload such as a D shaped ventricular septum, RA and RV dilation decreased TAPSE; when present increase the likelihood of PH being present even at pressures close to 30 mmHg. Data is available that a RVSP cut off of 38 mmHg had an acceptable sensitivity and a specificity of 82%, along with a PPV of 22%. If RV dilatation was added to this variable, then the sensitivity remained acceptable, and the specificity and PPV improved to 92% and 41% respectively [139, 140].

An echocardiography cannot report a LVEDP/PCWP or PVR thus a right heart catheterization remains important in diagnosis POPH and in differentiating POPH, hyperdynamic state due to liver disease with a low to normal PVR, and volume overload. When the mPAP is above 25 mmHg, with a low PCWP (below 15 mmHg), and the PVR is above 240 dynes/s/cm<sup>5</sup>, then in the right clinical setting the diagnosis of POPH can be made and it is presumed that the pathological changes of PAH are present in the pulmonary arterial system. If the PVR is below 240 dynes/s/cm<sup>5</sup>, even with a low PCWP and an elevated mPAP of above 25 mmHg, it is presumed that the PAH pathology is not present, the elevated mPAP in this case is related to the hyperdynamic state present in the liver disease (causing a higher blood flow through

the pulmonary vasculature) and not due to pulmonary arterial remodeling typical in PoPH and other PAH patients [48, 141–143]. If the RHC shows an elevated PCWP along with an elevated mPAP (and a normal trans pulmonary gradient) then the diagnosis of pulmonary venous congestion can be made just as in other forms of WHO Group II PH.

#### 11.6.5 Treatment

The goals of therapy in this patient population include symptomatic relief, improvement in exercise capacity, prolong survival and in a select group of patients facilitate liver transplantation. Based on data extrapolated from the general PAH population supplemental oxygen is universally used to prevent hypoxia [142], and diuretics are used to manage the overall volume status and also off load a dilated RV, specific to POPH these patients may already be on diuretics including Lasix and aldosterone to treat ascites. Volume status management in these patients can be challenging as they are also have decreased venous return and are prone to pre-renal azotemia along with hepato-renal syndrome.

While calcium channel blockers are reserved for a small group of IPAH patients who have a positive vasoreactivity test, in POPH they are contraindicated as they may cause splanchnic vasodilation worsen portal hypertension [144]. Beta blockers are used as prophylaxis for variceal hemorrhage, but at times is avoided them as they do have a negative chronotropic and inotropic effect, which may further decrease cardiac output and make the RV failure worse [145]. If atrial fibrillation is present and rate control is warranted digoxin should be considered, although dosing difficulties may arise given the changing renal function in these patients. When these patients have identified chronic pulmonary embolisms, it becomes difficult to pin point if the PAH is being caused by CTEPH or POPH. If anticoagulation is needed for proven chronic PE then the anticoagulant should be chosen based on the patient's individual's characteristics such as his/her baseline INR.

Identifying the correct patient for treating with PH specific therapy is extremely important just like other forms of pulmonary hypertension, if pulmonary vasodilators are given to the incorrect patient they may be of no benefit, and along with large financial cost to the patient at times may also cause worsening of symptoms. In a patient with an elevated mPAP, a normal PCWP and also a normal PVR (below 240 dynes/s/cm<sup>5</sup>), pulmonary vasodilators should not be used as the PH here is related to elevated CO caused by the liver disease and not due to pathology of the pulmonary arterial vasculature.

Patients with an elevated mPAP, normal PCWP and an elevated PVR (above 240 dynes/s/cm<sup>5</sup>) are candidates for PoPH specific therapies. POPH is not a direct indication to liver transplantation, pulmonary vasodilators can be used as



a definitive therapy to treat the POPH, or also as a bridge to transplantation. Prostanoids in the IV form, inhaled form or subcutaneous form [146–148] (epoprostanil, inhaled Ilioprost), endothelin receptor antagonists [149] (ERAs—Bosentan, Ambrisentan) and PDE5i [150] (Sildenafil, Tadalafil) have all been studied in the past with good outcomes. Of note ERAs, especially Bosentan can cause liver toxicity, and when used patients require close monitoring of their LFTs. The newer ERA Macitentan is reported to result in less elevation in LFTs.

These agents along with newer ones approved to treat PH are available to be used alone or in combination. The agents should be chosen based on the individual's disease severity, and ability to tolerate side effects, with the IV prostanoids reserved for the more severe disease. For WHO Functional class I–III patients oral or inhaled medications are suggested, either starting off with one agent or adding others as symptoms progress or they are started in combination. WHO Group III–IV patients along with oral and inhaled medications, IV or Subcutaneous prostanoids should be considered, keeping in mind the burden of care the patient has to direct towards these continuous treatments. Recently Selexipag [151] and oral prostanoid was approved in USA for use in WHO group I patients. It was tested mostly in patients with WHO functional class II–III patients. Although it is labeled to be used for all WHO Group I PAH which includes POPH, the studies using Selexipag so far have included idiopathic PAH and PAH related to connective tissue disease. It has not been tested in POPH.

The success rates for liver transplant in patient with mPAP between 25 mmHg and 35 mmHg have been excellent. A mPAP >45 mmHg and PVR > 400 dynes/s/cm<sup>2</sup> are absolute contraindications for LT, even with a mPAP >35 mmHg the peri-transplant mortality can be up to 50% [152]. In these patients, pulmonary vasodilators should be used to bring the mPAP below 35 mmHg, ideally even lower, and to bring the PVR ideally below 250 dynes/s/cm<sup>2</sup> before LT is attempted.

To accommodate patients with a mPAP 35 mmHg–45 mmHg in the liver transplant list a MELD exception was added in to the liver transplant scoring system. The system is detailed below [153].

- (a) The post PH specific treatment mean pulmonary artery pressure is below 35 mmHg or,
- (b) Pulmonary vascular resistance reduces to below 400 dynes/s/cm<sup>2</sup> regardless of mPAP and, satisfactory RV function by TTE (e.g. improvement in RV dilation and function).

If the above mentioned criteria are met then MELD exception score of a 22 is allocated to the patient with a 10% increase every 3 months, as long as mPAP remains below 35 mmHg as confirmed by repeat heart catheterization.

All PoPH patients should be referred to an experienced high volume center for pulmonary vasodilator therapy, and LT should be undertaken where invasive, intra-operative cardiac monitoring is possible with an experienced multidisciplinary team.

When POPH patients decompensate with respiratory or hemodynamic failure from processes such as sepsis, GI bleeding or with just progression of the disease they should be cared for in well-equipped and experienced intensive care units. Like in other forms of PAH, hypotension in POPH patients does not always mean they will respond to intravascular volume expansion, and often IV fluids resuscitation may even worsen the RV function. Case by case assessment at times with the help of invasive monitoring like the PA catheters along with other noninvasive evolution like the echocardiogram are necessary to direct adequate volume, pressor and inotrope requirements in these patients.

#### Box 11.1 Mechanisms of IPVD seen in HPS

1. Pulmonary NO overproduction—mediated by
  - Increased activity of eNOS and iNOS.
  - Increased expression of ET-B receptors in pulmonary vasculature.
  - Hepatic overproduction of Endothelin-1.
  - Pulmonary accumulation of macrophages induced by bacterial translocation and endotoxemia.
  - TNF-alpha.
2. Increased expression of Hemoxygenase and increase CO production
3. Activation of VEGF-associated signaling pathways and increased pulmonary angiogenesis.

#### Box 11.2 Characteristic features of uncomplicated hepatic hydrothorax

- Polymorphonuclear cell count <250 cells/mm<sup>3</sup>
- Total protein concentration < 2.5 g/dL
- Total protein pleural fluid to serum ratio < 0.5
- Lactate dehydrogenase pleural fluid to serum ratio < 0.6
- Serum to pleural fluid albumin gradient >1.1 g/dL
- Pleural fluid amylase concentration < serum amylase concentration
- Pleural fluid bilirubin/serum bilirubin <0.6
- Pleural fluid glucose level similar to that of serum level

## 11.7 Questions

- Which of the following is not a common mechanism of hypoxia in patients with liver disease?
  - Ventilation-perfusion mismatch
  - Diffusion impairment
  - Shunting
  - Alveolar hypoventilation
- Which mediator is primarily responsible for intrapulmonary vascular dilatations seen in HPS?
- What is the most sensitive test to detect IPVD in HPS?
- What is the only effective treatment that result in resolution of HPS or improvement in gas exchange?
- What is the treatment of choice for spontaneous bacterial pleuritis?
- A patient with underlying cirrhosis and portal hypertension complains of worsening SOB for about 3 months. Patient undergoes right heart catheterization which shows the following data. Three different scenarios are listed below. Please choose the appropriate diagnosis based on the RHC data:

mPAP (normal < 25 mmHg)	PVR (normal <240dynes/s/cm <sup>5</sup> )	PCWP (normal < 15 mmHg)	Diagnosis
35	300	10	
30	180	8	
30	220	20	

- Portpulmonary hypertension
- Hyperdynamic state associated with liver disease
- Volume overload

- An IAP above \_\_\_\_ mmHg can decrease perfusion of the gut and increase chances of ischemic damage and translocation of bacteria.
  - 5
  - 10
  - 15
  - 20

## References

- Karcz M, et al. Acute respiratory failure complicating advanced liver disease. *Semin Respir Crit Care Med*. 2012;33(1):96–110.
- Martinez GP, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol*. 2001;34(5):651–7.
- Moller S, et al. Arterial hypoxaemia in cirrhosis: fact or fiction? *Gut*. 1998;42(6):868–74.
- Astrup J, Rorth M. Oxygen affinity of hemoglobin and red cell 2,3-diphosphoglycerate in hepatic cirrhosis. *Scand J Clin Lab Invest*. 1973;31(3):311–7.
- Keys A, Snell AM. Respiratory properties of the arterial blood in normal man and in patients with disease of the liver: position of the oxygen dissociation curve. *J Clin Invest*. 1938;17(1):59–67.
- Agusti AG, et al. The lung in patients with cirrhosis. *J Hepatol*. 1990;10(2):251–7.
- Heinemann HO, Emirgil C, Mijnsen JP. Hyperventilation and arterial hypoxemia in cirrhosis of the liver. *Am J Med*. 1960;28:239–46.
- Rodman T, et al. Cyanosis, clubbing and arterial oxygen unsaturation associated with Laennec's cirrhosis. *Am J Med Sci*. 1959;238:534–41.
- Hoffbauer FW, Rydell R. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am J Med*. 1956;21(3):450–60.
- Massumi RA, Rios JC, Ticktin HE. Hemodynamic abnormalities and venous admixture in portal cirrhosis. *Am J Med Sci*. 1965;250(3):275–83.
- Mellemgaard K, et al. Sources of venoarterial admixture in portal hypertension. *J Clin Invest*. 1963;42:1399–405.
- Abelmann WH, et al. Cirrhosis of the liver and decreased arterial oxygen saturation. *Arch Intern Med*. 1961;108:34–40.
- Williams MH Jr. Hypoxemia due to venous admixture in cirrhosis of the liver. *J Appl Physiol*. 1960;15:253–4.
- Berthelot P, et al. Arterial changes in the lungs in cirrhosis of the liver–lung spider nevi. *N Engl J Med*. 1966;274(6):291–8.
- Nakamura T, et al. Measurement of blood flow through portopulmonary anastomosis in portal hypertension. *J Lab Clin Med*. 1965;65:114–21.
- Krowka MJ, Cortese DA. Pulmonary aspects of chronic liver disease and liver transplantation. *Mayo Clin Proc*. 1985;60(6):407–18.
- Furukawa T, et al. Arterial hypoxemia in patients with hepatic cirrhosis. *Am J Med Sci*. 1984;287(3):10–3.
- Ruff F, et al. Regional lung function in patients with hepatic cirrhosis. *J Clin Invest*. 1971;50(11):2403–13.
- Bell RC, et al. Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med*. 1983;99(3):293–8.
- Matuschak GM. Lung-liver interactions in sepsis and multiple organ failure syndrome. *Clin Chest Med*. 1996;17(1):83–98.
- Ruiter DJ, et al. Uptake by liver cells of endotoxin following its intravenous injection. *Lab Invest*. 1981;45(1):38–45.
- Wardle EN. Kupffer cells and their function. *Liver*. 1987;7(2):63–75.
- Bradfield JW. Control of spillover. The importance of Kupffer-cell function in clinical medicine. *Lancet*. 1974;2(7885):883–6.
- Nakao A, et al. The fate of intravenously injected endotoxin in normal rats and in rats with liver failure. *Hepatology*. 1994;19(5):1251–6.
- Katz S, et al. Impaired bacterial clearance and trapping in obstructive jaundice. *Ann Surg*. 1984;199(1):14–20.
- Yokoyama I, et al. Endotoxemia and human liver transplantation. *Transplant Proc*. 1989;21(5):3833–41.
- Miyata T, et al. Endotoxaemia, pulmonary complications, and thrombocytopenia in liver transplantation. *Lancet*. 1989;2(8656):189–91.
- Doyle RL, et al. Identification of patients with acute lung injury. Predictors of mortality. *Am J Respir Crit Care Med*. 1995;152(6 Pt 1):1818–24.
- Liang Y, Yeligar SM, Brown LA. Chronic-alcohol-abuse-induced oxidative stress in the development of acute respiratory distress syndrome. *ScientificWorldJournal*. 2012;2012:740308.
- Moss M, et al. The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):414–9.
- Rahman Q, et al. Glutathione redox system in oxidative lung injury. *Crit Rev Toxicol*. 1999;29(6):543–68.
- Johnson DH, Cunha BA. Infections in cirrhosis. *Infect Dis Clin N Am*. 2001;15(2):363–71. vii

33. Wallaert B, et al. Human alveolar macrophage antibacterial activity in the alcoholic lung. *Am Rev Respir Dis*. 1991;144(2):278–83.
34. Gosset P, et al. Impaired secretion and mRNA expression of monokines by alveolar macrophages from nonsmoking patients with alcoholic liver cirrhosis. *J Infect Dis*. 1995;171(3):743–6.
35. Fowler AA, et al. Adult respiratory distress syndrome. Prognosis after onset. *Am Rev Respir Dis*. 1985;132(3):472–8.
36. Hyers TM, Fowler AA. Adult respiratory distress syndrome: causes, morbidity, and mortality. *Fed Proc*. 1986;45(1):25–9.
37. Montgomery AB, et al. Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1985;132(3):485–9.
38. Seidenfeld JJ, et al. Incidence, site, and outcome of infections in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1986;134(1):12–6.
39. Das V, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. *Crit Care Med*. 2010;38(11):2108–16.
40. Findlay JY, et al. Critical care of the end-stage liver disease patient awaiting liver transplantation. *Liver Transpl*. 2011;17(5):496–510.
41. Phua J, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med*. 2009;179(3):220–7.
42. Saliba F, et al. Cirrhotic patients in the ICU: prognostic markers and outcome. *Curr Opin Crit Care*. 2013;19(2):154–60.
43. Zamboni M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest*. 2008;133(5):1120–7.
44. TenHoor T, Mannino DM, Moss M. Risk factors for ARDS in the United States: analysis of the 1993 National Mortality Followback Study. *Chest*. 2001;119(4):1179–84.
45. Schwartz LM, et al. Alcohol consumption, one-carbon metabolites, liver cancer and liver disease mortality. *PLoS One*. 2013;8(10):e78156.
46. Monchi M, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Am J Respir Crit Care Med*. 1998;158(4):1076–81.
47. Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. *Chest*. 1977;72(3):305–9.
48. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome – a liver-induced lung vascular disorder. *N Engl J Med*. 2008;358(22):2378–87.
49. Schenk P, et al. Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences. *Gut*. 2002;51(6):853–9.
50. Fallon MB, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology*. 2008;135(4):1168–75.
51. Cremona G, et al. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J*. 1995;8(11):1883–5.
52. Fallon MB, et al. The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. *Gastroenterology*. 1997;113(2):606–14.
53. Ling Y, et al. The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. *Hepatology*. 2004;39(6):1593–602.
54. Tang L, et al. Modulation of pulmonary endothelial endothelin B receptor expression and signaling: implications for experimental hepatopulmonary syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2007;292(6):L1467–72.
55. Rabiller A, et al. Prevention of gram-negative translocation reduces the severity of hepatopulmonary syndrome. *Am J Respir Crit Care Med*. 2002;166(4):514–7.
56. Thenappan T, et al. A central role for CD68(+) macrophages in hepatopulmonary syndrome. Reversal by macrophage depletion. *Am J Respir Crit Care Med*. 2011;183(8):1080–91.
57. Sztymf B, et al. Prevention of hepatopulmonary syndrome and hyperdynamic state by pentoxifylline in cirrhotic rats. *Eur Respir J*. 2004;23(5):752–8.
58. Zhang J, et al. Pentoxifylline attenuation of experimental hepatopulmonary syndrome. *J Appl Physiol* (1985). 2007;102(3):949–55.
59. Carter EP, et al. Regulation of heme oxygenase-1 by nitric oxide during hepatopulmonary syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2002;283(2):L346–53.
60. Zhang J, et al. Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. *Gastroenterology*. 2003;125(5):1441–51.
61. Zhang J, et al. Pulmonary angiogenesis in a rat model of hepatopulmonary syndrome. *Gastroenterology*. 2009;136(3):1070–80.
62. Abrams GA, et al. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology*. 1995;109(4):1283–8.
63. Krowka MJ, et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO<sub>2</sub>(2) response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. *Chest*. 2000;118(3):615–24.
64. Poterucha JJ, et al. Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy. *Hepatology*. 1995;21(1):96–100.
65. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: impact of liver transplantation. *Hepatology*. 2005;41(5):1122–9.
66. Arguedas MR, et al. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology*. 2003;37(1):192–7.
67. Goldberg DS, et al. Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: an analysis of the UNOS database. *Gastroenterology*. 2014;146(5):1256–65.e1.
68. Gupta S, et al. Improved survival after liver transplantation in patients with hepatopulmonary syndrome. *Am J Transplant*. 2010;10(2):354–63.
69. Ramalingam VS, Ansari S, Fisher M. Respiratory complication in liver disease. *Crit Care Clin*. 2016;32(3):357–69.
70. Huang PM, et al. The morphology of diaphragmatic defects in hepatic hydrothorax: thoracoscopic finding. *J Thorac Cardiovasc Surg*. 2005;130(1):141–5.
71. Lazaridis KN, et al. Hepatic hydrothorax: pathogenesis, diagnosis, and management. *Am J Med*. 1999;107(3):262–7.
72. Norvell JP, Spivey JR. Hepatic hydrothorax. *Clin Liver Dis*. 2014;18(2):439–49.
73. Strauss RM, Boyer TD. Hepatic hydrothorax. *Semin Liver Dis*. 1997;17(3):227–32.
74. Huang TW, et al. Education and imaging. Hepatobiliary and pancreatic: hepatic hydrothorax. *J Gastroenterol Hepatol*. 2007;22(6):956.
75. Malagari K, et al. Cirrhosis-related intrathoracic disease. Imaging features in 1038 patients. *Hepato-Gastroenterology*. 2005;52(62):558–62.
76. Benet A, et al. Diagnosis of hepatic hydrothorax in the absence of ascites by intraperitoneal injection of 99m-Tc-Fluor colloid. *Postgrad Med J*. 1992;68(796):153.
77. Rubinstein D, McInnes IE, Dudley FJ. Hepatic hydrothorax in the absence of clinical ascites: diagnosis and management. *Gastroenterology*. 1985;88(1 Pt 1):188–91.
78. Krok KL, Cardenas A. Hepatic hydrothorax. *Semin Respir Crit Care Med*. 2012;33(1):3–10.
79. Sahn SA. State of the art. The pleura. *Am Rev Respir Dis*. 1988;138(1):184–234.
80. Siegerstetter V, et al. Treatment of refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt:



- long-term results in 40 patients. *Eur J Gastroenterol Hepatol*. 2001;13(5):529–34.
81. Xiol X, et al. Usefulness and complications of thoracentesis in cirrhotic patients. *Am J Med*. 2001;111(1):67–9.
82. Feller-Kopman D, et al. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. *Ann Thorac Surg*. 2007;84(5):1656–61.
83. Chen CH, et al. Outcome predictors of cirrhotic patients with spontaneous bacterial empyema. *Liver Int*. 2011;31(3):417–24.
84. Liu LU, et al. Outcome analysis of cirrhotic patients undergoing chest tube placement. *Chest*. 2004;126(1):142–8.
85. Orman ES, Lok AS. Outcomes of patients with chest tube insertion for hepatic hydrothorax. *Hepatol Int*. 2009;3(4):582–6.
86. Gordon FD, et al. The successful treatment of symptomatic, refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt. *Hepatology*. 1997;25(6):1366–9.
87. Dhanasekaran R, et al. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. *Am J Gastroenterol*. 2010;105(3):635–41.
88. Wilputte JY, et al. The outcome after transjugular intrahepatic portosystemic shunt (TIPS) for hepatic hydrothorax is closely related to liver dysfunction: a long-term study in 28 patients. *Acta Gastroenterol Belg*. 2007;70(1):6–10.
89. Leveen HH, et al. Peritoneo-venous shunting for ascites. *Ann Surg*. 1974;180(4):580–91.
90. Kirsch WM, Newkirk JB, Predecki PK. Clinical experience with the Denver shunt: a new silicone-rubber shunting device for the treatment of hydrocephalus. Technical note. *J Neurosurg*. 1970;32(2):258–64.
91. Martin LG. Percutaneous placement and management of the Denver shunt for portal hypertensive ascites. *AJR Am J Roentgenol*. 2012;199(4):W449–53.
92. Chen TA, Lo GH, Lai KH. Risk factors for spontaneous bacterial empyema in cirrhotic patients with hydrothorax. *J Chin Med Assoc*. 2003;66(10):579–86.
93. Tu CY, Chen CH. Spontaneous bacterial empyema. *Curr Opin Pulm Med*. 2012;18(4):355–8.
94. Sese E, et al. Low complement levels and opsonic activity in hepatic hydrothorax: its relationship with spontaneous bacterial empyema. *J Clin Gastroenterol*. 2003;36(1):75–7.
95. Reed SF, et al. Aggressive surveillance and early catheter-directed therapy in the management of intra-abdominal hypertension. *J Trauma*. 2006; 61(6):1359–63; discussion 1363–5.
96. Ivatury RR, Diebel L. Intra-abdominal hypertension and the splanchnic bed. In: Cheatham M, Ivatury RR, Malbrain M, Sugrue M, editors. *Abdominal compartment syndrome*. Georgetown, TX: Landis Bioscience; 2006. p. 129–37.
97. Kovac N, Siranovic M, Mazul-Sunko B. Clinical significance of intraabdominal pressure and abdominal perfusion pressure in patients with acute abdominal syndrome. *Signa Vitae*. 2007;2(2):14–7.
98. Papavramidis TS, et al. Abdominal compartment syndrome – intra-abdominal hypertension: defining, diagnosing, and managing. *J Emerg Trauma Shock*. 2011;4(2):279–91.
99. Wendon J, Biancufiore G, Auzinger G. Intra-abdominal hypertension and the liver. In: Cheatham ML, Ivatury RR, Malbrain M, Sugrue M, editors. *Abdominal compartment syndrome*. Georgetown, TX: Landis Bioscience; 2006. p. 138–43.
100. Emerson H. Intra-abdominal pressures. *Arch Intern Med*. 1911;7:754–84.
101. Malbrain ML, De IE. laet, Intra-abdominal hypertension: evolving concepts. *Clin Chest Med*. 2009;30(1):45–70. viii
102. Lui F, Sangosanya A, Kaplan LJ. Abdominal compartment syndrome: clinical aspects and monitoring. *Crit Care Clin*. 2007;23(3):415–33.
103. Cheatham ML, Malbrain M. Intra-abdominal hypertension and the cardiovascular system. In: Cheatham M, Ivatury RR, Malbrain M, Sugrue M, editors. *Abdominal compartment syndrome*. Georgetown, TX: Landis Bioscience; 2006. p. 89–104.
104. Ropper AH, Samuels MA, and York NY. Disturbances of cerebrospinal fluid and its circulation including hydrocephalus, pseudotumor cerebri, and low-pressure syndromes. Vol. 2009 SRC – GoogleScholar. 2009. 529–545.
105. Malbrain ML, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I Definitions. *Intensive Care Med*. 2006;32(11):1722–32.
106. Malbrain M, et al. Intra-abdominal pressure measurement techniques. In *Abdominal compartment syndrome* Landis Bioscience, 2006. 2006 SRC – GoogleScholar; p. 19–68.
107. Papavramidis TS, et al. Abdominal compliance, linearity between abdominal pressure and ascitic fluid volume. *J Emerg Trauma Shock*. 2011;4(2):194–7.
108. De Keulenaer BL, et al. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? *Intensive Care Med*. 2009;35(6):969–76.
109. Hakobyan RV, Mkhoyan GG. Epidural analgesia decreases intraabdominal pressure in postoperative patients with primary intra-abdominal hypertension. *Acta Clin Belg*. 2008;63(2): 86–92.
110. Levesque E, et al. Outcome of patients with cirrhosis requiring mechanical ventilation in ICU. *J Hepatol*. 2014;60(3):570–8.
111. Shellman RG, et al. Prognosis of patients with cirrhosis and chronic liver disease admitted to the medical intensive care unit. *Crit Care Med*. 1988;16(7):671–8.
112. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000; 342(18):1301–8.
113. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2013;2:CD003844.
114. Funk GC, et al. Acid-base disturbances in critically ill patients with cirrhosis. *Liver Int*. 2007;27(7):901–9.
115. Girard TD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126–34.
116. Kress JP, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471–7.
117. Payen J-F, et al. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. *Anesthesiology*. 2009;111(6):1308–16.
118. Payen JF, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology*. Apr quiz 8912 17413906, 2007. 106(4 SRC – GoogleScholar): 687–95.
119. Nagai S, et al. Noninvasive positive pressure ventilation to prevent respiratory collapse after extubation: clinical case reports. *Transplant Proc*. 2009;41(9):3919–22.
120. Narita M, et al. Prophylactic respiratory management after liver resection with bilevel positive airway pressure ventilation: report of three cases. *Surg Today*. 2009;39(2):172–4.
121. Mantz FA Jr, Craige E. Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. *AMA Arch Pathol*. 1951;52(1):91–7.
122. Simonneau G, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34–41.

123. McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? *Am Rev Respir Dis*. 1983;127(4):437–41.
124. Krowka MJ, et al. Portopulmonary hypertension: results from a 10-year screening algorithm. *Hepatology*. 2006;44(6):1502–10.
125. Hadengue A, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology*. 1991;100(2):520–8.
126. Colle IO, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology*. 2003;37(2):401–9.
127. Krowka MJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. *Chest*. 2012;141(4):906–15.
128. Le Pavec J, et al. Portopulmonary hypertension: survival and prognostic factors. *Am J Respir Crit Care Med*. 2008;178(6):637–43.
129. Medarov BI, Chopra A, Judson MA. Clinical aspects of portopulmonary hypertension. *Respir Med*. 2014;108(7):943–54.
130. Pilatis ND, et al. Clinical predictors of pulmonary hypertension in patients undergoing liver transplant evaluation. *Liver Transpl*. 2000;6(1):85–91.
131. Robalino BD, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. *J Am Coll Cardiol*. 1991;17(2):492–8.
132. Benjaminov FS, et al. Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *Gut*. 2003;52(9):1355–62.
133. Kamath PS, et al. Hepatic localization of endothelin-1 in patients with idiopathic portal hypertension and cirrhosis of the liver. *Liver Transpl*. 2000;6(5):596–602.
134. Neuhofer W, et al. Endothelin and endothelin receptor antagonism in portopulmonary hypertension. *Eur Invest Sep 36 Suppl Review* 1692, 1901. 3 SRC – Google Scholar: 54–61.
135. Tuder RM, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med*. 1999;159(6):1925–32.
136. Hervé P, et al. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med*. 1995;99(3):249–54.
137. Edwards BS, et al. Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol*. 1987;10(6):1233–8.
138. Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. *Liver Transpl*. 2000;6(2):241–2.
139. Porres-Aguilar M, Duarte-Rojó A, Krowka MJ. Transthoracic echocardiography screening for the detection of portopulmonary hypertension: a work in progress. *Liver Transpl*. 2013;19(6):573–4.
140. Raevens S, et al. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. *Liver Transpl*. 2013;19(6):602–10.
141. Cartin-Ceba R, Krowka MJ. Portopulmonary hypertension. *Clin Liver Dis*. 2014;18(2):421–38.
142. Porres-Aguilar M, et al. Portopulmonary hypertension and hepatopulmonary syndrome: a clinician-oriented overview. *Eur Respir Rev*. 2012;21(125):223–33.
143. Porres-Aguilar M, et al. Portopulmonary hypertension: state of the art. *Ann Hepatol*. 2008;7(4):321–30.
144. Ota K, et al. Effects of nifedipine on hepatic venous pressure gradient and portal vein blood flow in patients with cirrhosis. *J Gastroenterol Hepatol*. 1995;10(2):198–204.
145. Provencher S, et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterology*. 2006;130(1):120–6.
146. Fix OK, et al. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. *Liver Transpl*. 2007;13(6):875–85.
147. Krowka MJ, et al. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology (Baltimore, MD)*. 1999;30(3):641–8.
148. Sussman N, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. *Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg*. 2006;6(9):2177–82.
149. Hoepfer MM, et al. Bosentan therapy for portopulmonary hypertension. *Eur Respir J*. 2005;25(3):502–8.
150. Reichenberger F, et al. Sildenafil treatment for portopulmonary hypertension. *Eur Respir J*. 2006;28(3):563–7.
151. Sitbon O, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522–33.
152. Krowka MJ, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl*. 2004;10(2):174–82.
153. Krowka MJ, et al. Model for end-stage liver disease (MELD) exception for portopulmonary hypertension. *Liver Transpl*. 2006;12(12 Suppl 3):S114–6.



Constantine J. Karvellas, Francois Durand,  
Mitra K. Nadim, and Kai Sigbartl

## Abstract

Acute Kidney Injury (AKI) is common complication of acute and chronic liver disease. Hepatorenal syndrome is a severe consequence of advanced cirrhosis and occurs due to intense renal vasoconstriction causing a reduction in renal perfusion and glomerular filtration. The evaluation of renal dysfunction in cirrhosis is challenging because of the poor correlation of commonly used indices of kidney function to glomerular filtration rate. Novel biomarkers hold promise for the early diagnosis and prognosis of acute kidney injury in cirrhosis but are yet in clinical use. Therapies for acute kidney injury include vasoconstrictors, albumin and liver transplantation. Renal replacement therapy should be used as a bridge to liver transplant.

## Keywords

Acute on chronic liver failure • Acute kidney injury • Cirrhosis • Hepatorenal syndrome

## Abbreviations

ACLF	Acute on chronic liver failure	ICA	International Ascites Club
ADQI	Acute Dialysis Quality Initiative	ICU	Intensive care unit
AKI	Acute kidney injury	INR	Internationalized ratio
AKIN	Acute kidney injury network	KDIGO	Kidney disease improving global outcome
CRRT	Continuous renal replacement therapy	LT	Liver transplantation
GFR	Glomerular filtration rate	MELD	Modified end stage Liver Disease score
HRS	Hepatorenal syndrome	RIFLE	Risk, injury, failure, loss, end stage renal disease
		RRT	Renal replacement therapy
		sCr	Serum creatinine
		TIPS	Transjugular intrahepatic portosystemic shunt

**Permissions:** This chapter was adapted/modified (with permission) from *Acute Kidney Injury in Cirrhosis*. Karvellas CJ, Durand F, Nadim MK. *Crit Care Clin*. 2015 Oct;31(4):737–50. PMID: 26,410,141, with permission from Elsevier (publisher).

C.J. Karvellas, M.D., S.M., F.R.C.P.C. (✉)  
Department of Critical Care Medicine, University of Alberta,  
Edmonton, Canada

Division of Gastroenterology, Faculty of Medicine and Dentistry,  
University of Alberta, Edmonton, Canada  
e-mail: [dean.karvellas@ualberta.ca](mailto:dean.karvellas@ualberta.ca)

F. Durand  
Hepatology and Liver Intensive Care Unit, Hospital Beaujon,  
Clichy, France

INSERM U1149 and University Paris VII, Denis Diderot, France

M.K. Nadim  
Division of Nephrology, Department of Medicine, Keck School of  
Medicine, University of Southern California,  
Los Angeles, CA, USA

K. Sigbartl  
Department of Anaesthesia and Critical Care, Penn State, Hershey,  
Hershey, PA, USA

## 12.1 Introduction

Renal failure or *acute kidney injury (AKI)* is a common complication of acute and chronic liver disease, especially those with acute on chronic liver failure (ACLF), occurring in up to 50% of hospitalized patients with cirrhosis [1–5]. The high incidence of AKI is polyfactorial, due to the combination of arterial vasodilation with increased intra-renal vasoconstriction and impaired renal auto regulation which predisposes to renal dysfunction, and a number of precipitating factors related to cirrhosis, typically bacterial infections and gastrointestinal bleeding [6–8]. There is currently no specific blood or urine biomarker that can reliably identify the cause of AKI in cirrhotic patients. Traditional diagnostic criteria focused particular attention to **hepatorenal syndrome (HRS)** and its physiology of renal vasoconstriction and splanchnic vasodilatation [9] with criteria based on elevation in serum creatinine (sCr) > 50% over baseline with value >133  $\mu\text{mol/L}$  (1.5 mg/dL). Irreversibility of HRS has been shown to have a deleterious impact on mortality [10]. However, subsequent studies have questioned these criteria as narrow and require a broader look at other causes of AKI in liver disease [5].

### 12.1.1 Epidemiology

Classification of renal dysfunction in cirrhotic patients can be based on acuity of presentation (acute, chronic or acute on chronic) however the majority of cirrhotic patients (~70%) have AKI without structural changes [11]. Causes of AKI include hypovolemia/prerenal azotemia, intrinsic renal/parenchymal disorders (acute tubular necrosis/ATN, nephrotoxicity, interstitial nephritis, glomerulonephritis/nephropathy), obstructive nephropathy and hepatorenal syndrome [12].

### 12.1.2 Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a severe complication of advanced cirrhosis. Its clinical manifestations are related to derangements in renal, hepatic and the systemic circulation. HRS is a consequence of intense renal vasoconstriction leading to a reduction in renal perfusion and glomerular filtration. Renal excretion of sodium and free water is also impaired without histological changes. HRS has been described in two different clinical patterns, according to intensity and timing. Traditionally, **Type 1 HRS** increasingly represents the severe end of the spectrum of renal failure in cirrhosis. It is characterized by rapidly progressive renal failure with oliguria. It is defined as a doubling of the serum creatinine level to >2.5 mg/dL or a 50% reduction in 24-h creatinine clearance to a level <20 mL/min in less than 2 weeks. **Type II HRS** progresses slowly and represents a less severe deterioration in renal func-

tion that may remain stable for extended periods of time. Type II HRS is typically associated with refractory ascites. This is the result of sodium retention, reduced glomerular filtration and marked stimulation of the renin-angiotensin system. Recently, the International Ascites Club (ICA) in 2011 revised traditional criteria to define HRS type acute kidney injury (**HRS-AKI**) as including diagnosis of cirrhosis with ascites, increase in sCr by 50% with final sCr value >133  $\mu\text{mol/L}$  (1.5 mg/dL), no response to diuretic withdrawal/plasma expansion with albumin 1 g/kg per body weight, absence of shock, absence of nephrotoxins (NSAIDs, iodinated contrast) and an absence of macroscopic signs of structural kidney disease [13].

### 12.1.3 Circulatory Dysfunction and HRS

HRS is derived primarily from *circulatory failure*. According to the *peripheral vasodilatation model*, in cirrhosis the decrease in splanchnic and systemic arterial vascular resistance is likely related to increased expression of endothelial nitric oxide synthase and the concentration of nitric oxide and its metabolites in the splanchnic as well as systemic circulation [14]. In contrast, the production of nitric oxide in the intrahepatic circulation is reduced, exacerbating portal hypertension. The resultant decreased mean arterial pressure (MAP) and low total systemic vascular resistance is offset initially in compensated cirrhosis by an increase in cardiac output. In contrast to splanchnic blood flow, other vascular beds such as the cerebral, renal and hepatic beds demonstrate an increase in resistance. The kidneys are initially able to compensate by increasing production renal prostaglandins, resulting in renal vasodilation and preservation of renal perfusion and function. When cardiac output can no longer compensate, hypovolemia occurs with subsequent activation of the renin-angiotensin, vasopressin and sympathetic nervous systems. In particular, angiotensin II plays a central role in stimulating renal vasoconstriction while increasing release of aldosterone, leading to increased sodium retention and ascites. As hepatic failure progresses and splanchnic vasodilation predominates, the heightened effects of potent renal vasoconstrictors (angiotensin II, endothelin, norepinephrine and arginine-vasopressin) override the effect of local renal prostaglandins. This imbalance eventually results in HRS [15].

HRS may occur spontaneously with worsening liver function, or secondary to a precipitating event, such as spontaneous bacterial peritonitis (SBP). Approximately one third of patients with SBP develop renal impairment in the absence of nephrotoxic antibiotics and shock. For some of these patients, renal impairment is reversible with appropriate antimicrobial therapy but for the majority it is not. Other precipitating causes include large volume therapeutic paracentesis without albumin replacement, diuretic use in refractory ascites and gastrointestinal bleeding (especially with shock) [2].

### 12.1.4 Pathophysiology of AKI in Cirrhosis: Inflammation?

While several publications have made reference to dysregulation of the renin-angiotensin system, sympathetic nervous system and antidiuretic hormone production in the development of AKI and cirrhosis, inflammation in the presence or absence of infection plays a prominent role. Cirrhotic patients are at high risk of bacterial translocation leading to increased circulating levels of lipopolysaccharide-binding protein, increasing production of tumor-necrosis factor alpha which exacerbates splanchnic vasodilation. Other important immunological factors triggered by hepatic injury include release of damage associated molecular pattern (DAMP) compounds including high mobility group box-one (HMGB-1). This DAMP interacts through toll-like receptors (TLR) 2 and 4 causing subsequent renal tubule injury [16, 17].

### 12.1.5 Assessment of Renal Dysfunction

Evaluation of renal function in patients with cirrhosis remains a challenging problem. Serum creatinine (sCr) remains the most commonly used clinical index of kidney function however it is influenced by a variety of factors including age, muscle mass, gender and ethnicity. In liver cirrhosis sCr overestimates renal function due to decreased creatine production by the liver, protein calorie malnutrition, and muscle wasting, thus, a sCr within the normal range does not exclude significant renal impairment. In addition, sCr values may vary widely in patients with ascites because of dilutional changes in volume status after paracentesis and with the use of diuretics. High serum bilirubin levels may affect the assays used for measurement of sCr resulting in falsely low serum creatinine concentrations. Glomerular filtration rate (GFR) is considered the best estimate of renal function although there is no universally accepted gold standard for measurement of GFR. GFR can be measured by creatinine clearance with timed urinary collection and determination of urinary and serum creatinine concentration. However, in addition to inherent limitations related to inaccurate or incomplete urine collection, increased tubular secretions of creatinine may bias creatinine clearance as GFR declines in cirrhosis [18, 19]. In patients with cirrhosis, creatinine clearance tends to overestimate true GFR. The Modified Diet in Renal Disease (MDRD) [20] equations are widely used to estimate GFR in the general population but MDRD-4 consistently overestimate GFR in cirrhotic patients [21, 22]. Among creatinine-based equations, it has been shown that MDRD-6 is the most accurate in cirrhosis [23]. However, in contrast to MDRD-4, MDRD-6 may underestimate true GFR, discordances being more pronounced in old patients and patients with low serum sodium. Other indirect markers of renal

function such as Cystatin C are available however; they are costly, not widely available and recent studies have shown that like  $S_{Cr}$ , cystatin C is affected by muscle mass and liver disease and overestimates renal function in patients with cirrhosis [24, 25]. Equations based on cystatin C, with or without creatinine, may be superior to creatinine-based eq. [26, 27]. Again, the performance of current cystatin C-based equations (i.e., CKD-EPI creatinine-cystatin C equation) in patients with cirrhosis is inferior to that observed in the general population. In more than 20% of cirrhotic patients, a discordance of more than 30% is observed between cystatin C-based equations and true GFR [26].

The clearance of exogenous markers such as iothalamate, inulin or radioisotopes, are the most accurate methods of GFR assessment (see Table 12.1). However, they are not routinely used in clinical practice, for reasons of cost, convenience and availability. Despite these limitations, direct measurement of GFR with exogenous markers should be an absolute prerequisite for making a decision for combined liver and kidney transplantation rather than liver transplantation alone.

### 12.1.6 AKI in Patients with Liver Disease: Definitions

In 2004, the Acute Dialysis Quality Initiative (ADQI) Workgroup developed a consensus definition and classification for AKI known as the RIFLE criteria, which stratified acute renal dysfunction into grades of increasing severity based on changes in serum creatinine and/or urine output [28]. Subsequently, the Acute Kidney Injury Network (AKIN), proposed to broaden the definition of AKI to include an absolute increase in serum creatinine of  $\geq 0.3$  mg/dL (26  $\mu$ mol/L) when documented to occur within 48 h [29]. Once AKI is established, a staging system then defines the severity of the AKI. These criteria were then adopted by the international multidisciplinary Kidney Disease Improving Global Outcomes (KDIGO) in their 2012 clinical practice guideline [30] (see Table 12.2). In 2010, the ADQI workgroup along with several members of the International Ascites Club (IAC) recommended adaptation of the modified RIFLE criteria to define AKI in patients with cirrhosis instead of the traditional definition using a fixed serum creatinine ( $S_{Cr}$ ) cut off value of greater than 1.5 mg/dL [13, 31]. These criteria are irrespective of whether the presumed cause of the acute deterioration in renal function is related to a functional or structural disorder. As such, hepatorenal syndrome (HRS) type 1 was categorized as a specific type of AKI while HRS type 2 a form of acute on CKD and the term hepatorenal disorders (HRD), was proposed to encompass the full range of conditions where liver and kidney disease coexist. Since then, the use of AKIN criteria in predicting mortality has been validated in several studies of hospitalized patients with cirrhosis including those in the intensive care units [2, 3, 32, 33].

**Table 12.1** Methods of assessing renal function in liver disease

		Advantages	Disadvantages
<i>Serum based methods</i>	<b>Serum Creatinine</b>	<ul style="list-style-type: none"> <li>• Universally available</li> <li>• Inexpensive</li> <li>• MELD/AKI scores, current HRS definitions use this</li> </ul>	<ul style="list-style-type: none"> <li>• Affected by age, gender, muscle mass, steroids, medications</li> <li>• Decreased generation in liver disease</li> <li>• Bilirubin effect on assay</li> <li>• Lack of standardization of creatinine assays</li> <li>• Slow to rise in AKI</li> </ul>
	<b>Serum Cystatin C</b>	<ul style="list-style-type: none"> <li>• Not affected by age, gender, muscle mass, sepsis</li> <li>• Simple blood test</li> <li>• Appears to detect early kidney dysfunction and AKI earlier than serum creatinine</li> </ul>	<ul style="list-style-type: none"> <li>• Underestimates GFR post transplant</li> <li>• Dilution as with all serum markers</li> <li>• Variable performance of Cystatin C</li> <li>• Variable expense</li> <li>• Results may not be available on a timely fashion</li> </ul>
<i>Clearance based methods</i>	<b>Urinary creatinine clearance</b>	<ul style="list-style-type: none"> <li>• Inexpensive</li> <li>• Avoids dilution issues of serum markers</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult to get accurate collections</li> <li>• Systematically Overestimates GFR in liver disease by 10–15% especially in pts. with chronic kidney disease</li> </ul>
	<b>Inulin</b>	<ul style="list-style-type: none"> <li>• Still considered ‘gold standard’</li> </ul>	<ul style="list-style-type: none"> <li>• Systematic plasma clearance overestimates GFR</li> <li>• Cumbersome</li> </ul>
	<b>Iothalamate</b>	<ul style="list-style-type: none"> <li>• As good as inulin in most studies</li> </ul>	<ul style="list-style-type: none"> <li>• Significant extra-renal clearance</li> <li>• Shown to overestimate GFR by 10–20 ml/min</li> </ul>
	<b>CrEDTA</b>	<ul style="list-style-type: none"> <li>• As good as inulin in most studies</li> </ul>	<ul style="list-style-type: none"> <li>• Significant extra-renal clearance</li> <li>• Shown to overestimate GFR by 10–20 ml/min</li> </ul>
	<b>DcDPTA</b>	<ul style="list-style-type: none"> <li>• As good as inulin in most studies</li> </ul>	<ul style="list-style-type: none"> <li>• Significant extra-renal clearance</li> </ul>

(Adapted from, Acute Kidney Injury in Cirrhosis. Karvellas CJ, Durand F, Nadim MK. Crit Care Clin. 2015 Oct;31(4):737–50. PMID: 26,410,141, with permission from Elsevier (publisher))

### 12.1.7 AKI in Cirrhosis: Novel Biomarkers

Given the limitations of calculating GFR with current available laboratory tests and techniques, other novel renal biomarkers have recently been investigated to not only diagnose AKI earlier and more accurately but potentially also to shed light on etiology (i.e. differentiating ATN vs. HRS-AKI). There are several *urinary* biomarkers associated with tubular damage. Neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, Kidney-injury molecule-1 (KIM-1) and liver type fatty acid binding protein (L-FABP) are associated with renal tubular injury. In a recent study of 110 cirrhotic patients with AKI who were retrospectively identified as having prerenal azotemia, HRS or ATN, NGAL, KIM-1, IL-17 and L-FABP were significantly higher in patients with ATN than HRS/prerenal azotemia [34]. This suggests that these tubular biomarkers may identify patients who are less likely to benefit from volume resuscitation and vasopressor therapy, although one caveat is urinary tract infection may confound NGAL levels [35].

Renal biomarkers predictive of recovery from AKI following liver transplantation could enhance decision algorithms regarding the need for liver-kidney transplantation

or renal sparing regimens. Levitsky et al. recently published a pilot study of 16 patients, which showed that plasma proteins osteopontin, NGAL, Cystatin-C, TFF3, TIMP-1,  $\beta$ -2-microglobulin were higher in patients with reversible AKI post-LT compared in patients without AKI ( $p < 0.05$ ). Furthermore in a validation set of 46 patients, osteopontin and TIMP-1 were significantly higher in patients with reversible AKI post-LT than in irreversible AKI post-LT [36].

### 12.1.8 Therapies: Hepatorenal Syndrome

While liver transplantation (LT) is the only definitive treatment for HRS, it is clear that patients with renal failure at the time of transplant have poorer outcomes than those that do not. Furthermore, the longer the duration of renal dysfunction pre-transplant is associated with poorer post-transplant renal recovery. The main purpose of treatments investigated for HRS is to provide a bridge to transplant. To date, therapies that have been evaluated include albumin, vasoconstrictor therapy, transjugular intrahepatic portosystemic shunt (TIPS) and extracorporeal liver support.



**Table 12.2** Diagnostic criteria for Acute Kidney Injury (AKI) in cirrhosis

	RIFLE Criteria [59]	AKIN Criteria [29]	KDIGO Criteria [30]	ICA: AKI in Cirrhosis [13]
<b>Diagnostic Criteria</b>	Increase in sCr to $\geq 1.5$ times baseline, within 7 days; or GFR decrease $>25\%$ ; or Urine volume $< 0.5$ ml/kg/h for 6 h	Increase in sCr by $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/L}$ ) within 48 h; or Increase in sCr $\geq 1.5$ times baseline within 48 h; or Urine volume $< 0.5$ ml/kg/h for 6 h	Increase in sCr by $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/L}$ ) within 48 h; or Increase in sCr to $\geq 1.5$ times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume $< 0.5$ ml/kg/h for 6 h	A percentage increase in sCr of 50% or more to a final value of sCr $>1.5$ mg/dl (133 $\mu\text{mol/L}$ )
<b>Staging</b>	<b>Risk:</b> sCr increase 1.5–1.9 times baseline; or GFR decrease 25–50%; or Urine output $<0.5$ ml/kg/h for 6 h	<b>Stage 1:</b> sCr increase 1.5–1.9 times baseline; or sCr increase $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/L}$ ); or Urine output $<0.5$ ml/kg/h for 6 h	<b>Stage 1:</b> sCr increase 1.5–1.9 times baseline; or Cr increase $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/L}$ ); or Urine output $<0.5$ ml/kg/h for 6–12 h	
	<b>Injury:</b> sCr increase 2.0–2.9 times baseline; or GFR decrease 50–75%; or Urine output $<0.5$ ml/kg/h for 12 h	<b>Stage 2:</b> sCr increase 2.0–2.9 times baseline; or Urine output $<0.5$ ml/kg/h for 12 h	<b>Stage 2:</b> sCr increase 2.0–2.9 times baseline; or Urine output $<0.5$ ml/kg/h for $\geq 12$ h	
	<b>Failure:</b> sCr increase $\geq 3.0$ times baseline; or GFR decrease 50–75%; or sCr increase $\geq 4.0$ mg/dl (353.6 $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dl (44 $\mu\text{mol/L}$ ); or Urine output $<0.3$ ml/kg/h for $\geq 24$ h; or Anuria for $\geq 12$ h	<b>Stage 3:</b> sCr increase 3.0 times baseline; or sCr increase $\geq 4.0$ mg/dl (353.6 $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dl (44 $\mu\text{mol/L}$ ); or Urine output $<0.3$ ml/kg/h for $\geq 24$ h; or Anuria for $\geq 12$ h	<b>Stage 3:</b> sCr increase 3.0 times baseline; or sCr increase to $\geq 4.0$ mg/dl (353.6 $\mu\text{mol/L}$ ); or Initiation of RRT; or Urine output $<0.3$ ml/kg/h for $\geq 24$ h; or Anuria for $\geq 12$ h	

AKIN Acute Kidney Injury Network, GFR glomerular filtration rate, KDIGO Kidney Disease Improving Global Outcome, RIFLE Risk, Injury, Failure, Loss, End stage renal disease, sCr serum creatinine

Adapted from (with permission) *Angeli et al., Journal of Hepatology 2015 (Publisher Elsevier [60])*

### 12.1.9 Albumin

Administration of albumin in cirrhotics also has been shown to cause arterial vasoconstriction in patients with SBP, possibly due to the ability of albumin to bind vasodilators such as nitric oxide [37]. This forms the basis for the use of extracorporeal liver support in HRS (see below). Previous studies have shown that albumin prevented type 1 HRS in SBP patients with a typical dose of 1 g/kg (20–25%) on day one, then 20–60 g/day thereafter [38]. Adding albumin to other pharmacological therapies likely provides the most benefit.

#### 12.1.10 Vasoconstrictor Therapy: Vasopressin Analogues

Vasoconstrictor therapies have been relatively well studied in the treatment of HRS and in particular, **vasopressin** analogues. The high prevalence of  $V_1$  receptors in the splanchnic vasculature makes it especially sensitive to the vasoconstrictive effect of vasopressin analogues and therefore it is an important target for HRS therapy. The net theoretical result would be an increase in effective circulating arterial blood

volume and suppression of the renin-angiotensin system and the sympathetic nervous system, resulting in renal afferent vasodilatation. **Terlipressin** has a strong affinity towards the  $V_1$  receptors with a longer half-life and can be dosed intermittently. In two randomized controlled studies (2008) in patients with type 1 HRS comparing albumin vs. terlipressin plus albumin, HRS reversal occurred significantly more frequently in the terlipressin group. Furthermore, survival in patients responding to treatment was longer than in those who did not [1, 39]. Furthermore, a recent meta-analysis of 5 trials evaluating terlipressin for Type 1 HRS showed mortality was 48% in patients who received terlipressin alone or terlipressin with albumin, vs. 64% in patients randomized to no intervention placebo, or albumin alone; it thus reduce mortality with a relative risk (RR) of 0.76 [40]. The assessment of mortality was limited due to small numbers and short follow-up (1–6 months). Cardiovascular adverse events were higher in terlipressin patients [40]. Finally, a recent prospective study that included 18 patients with type 1 HRS and sepsis that received terlipressin and albumin showed that there was a significant improvement in arterial blood pressure and suppression of high renin levels and norepinephrine. Improvement of renal function was observed in 67% of

the patients and was associated with an improved 3-month survival compared to patients without response. Patients who did not respond had a higher MELD and Child–Pugh scores, and higher CLIF-SOFA [41].

Terlipressin should be dosed progressively, starting at 0.5 mg intravenous every four hours. If the serum creatinine does not decrease by 30% in 3 days, the dose should be doubled. In general, a patient not responding to 12 mg/day will not respond to higher doses. In patients who respond to terlipressin, treatment should be continued until normalization of serum creatinine (<1.5 mg/dL).

### 12.1.11 Vasoconstrictor Therapy: Norepinephrine

Early uncontrolled pilot data showed that titrating norepinephrine to achieve a MAP increase of 10 mmHg was associated with improved urine output, sodium excretion and creatinine clearance. Two controlled studies have compared the efficacy of norepinephrine versus terlipressin. In one study of 22 patients with HRS (type I  $n = 9$ , type II  $n = 13$ ), patients received albumin plus; norepinephrine 0.1–0.7  $\mu\text{g/kg/min}$  intravenous infusion or terlipressin 1–2 mg every four hours. Reversal of HRS occurred in 70% of patients receiving norepinephrine vs. 83% of patients receiving terlipressin ( $P = \text{NS}$ ) [42]. A second study compared albumin with norepinephrine (8–50  $\mu\text{g/min}$  intravenous) or terlipressin (0.5–2.0 mg every six hours) in 20 patients with type 1 HRS. The number of patients that responded to therapy did not significantly differ between the two groups (50% to 40%,  $p = 0.7$ ) and furthermore there was no significant difference in cumulative survival [43]. These results suggest that norepinephrine may be a safe and non-inferior alternative to vasopressin analogues in the treatment of HRS. A recent systematic review examined the major vasoconstrictors available for HRS, focusing on terlipressin and norepinephrine. In this review of four studies and a total of 154 patients, it was found that terlipressin and norepinephrine appeared to be equivalent in terms of HRS reversal, mortality at 30 days, and recurrence of HRS. Of note, adverse events were less frequent in patients who received norepinephrine [44].

**Midodrine** is an orally administered alpha-adrenergic agonist that appears to be beneficial in HRS. Its oral preparation makes it a feasible option for patients who are not in intensive care but require long-term vasoconstrictor therapy. It is often given in combination with **octreotide**, a long-acting somatostatin analogue, which reduces portal hypertension and splanchnic hyperemia. It may cause splanchnic vasoconstriction through inhibition of glucagon synthesis or a direct effect on vascular smooth muscle. In a recent observational study, 75 patients received a mean of 8 days of midodrine (7.5–12.5 mg orally three times daily), subcutaneous

octreotide (100–200  $\mu\text{g}$  subcutaneously three times daily) and intravenous albumin (50–100 g intravenous daily). The treatment group was compared with a historical control group of 87 patients with type 1 or 2 HRS who did not receive these therapies. Median survival was significantly improved in both type 1 HRS (40 vs. 17 days,  $p = 0.007$ ) and type 2 (>12 months vs. 22 days  $p = 0.0004$ ) with more type 2 HRS patients in the treatment group undergoing liver transplant (58 vs. 25%,  $p = 0.04$ ) [45].

### 12.1.12 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

In theory, the benefit of TIPS is by decreasing portal hypertension with a subsequent decrease in concentration of vasoconstrictory mediators (vasopressin, norepinephrine, endothelin and angiotensin II). The role of TIPS has been evaluated in small pilot studies. In seven cirrhotics patients with type 1 HRS who underwent TIPS, six of seven patients had improvement in serum creatinine and blood urea nitrogen at day 30. Reductions in plasma renin and norepinephrine levels were also noted [46]. In a prospective controlled study of 41 non-transplantable cirrhotics with HRS (type 1  $n = 21$ , type 2  $n = 20$ ), thirty-one patients (type 1  $n = 14$ , type 2  $n = 17$ ) received TIPS while 10 patients with advanced liver failure were excluded from a shunt (type I  $n = 7$ , type 2  $n = 3$ ). TIPS was associated with improved renal function with 2 weeks (creatinine clearance 18 to 48 ml/min,  $p < 0.001$ ) and stabilized thereafter. Following TIPS, at three, six, 12, and 18 months survival rates were 81%, 71%, 48%, and 35% respectively. These were significantly higher than in the non-shunted group (log rank 18.3,  $p < 0.001$ ) [47]. Unfortunately, in the majority of cirrhotic patients with HRS, TIPS is contraindicated due to severity of hepatic dysfunction (e.g. MELD >20) and the risk of further deterioration.

#### Renal Replacement Therapy.

The role of intermittent or continuous renal replacement therapy (RRT) in HRS is primarily as a bridge to LT. Observational studies have shown that RRT is not predictive of improved transplant free survival. The use of RRT in patients with HRS is likely only appropriate in the setting of a patient who is listed for LT or has another indication for RRT (i.e. uremia, acidosis, hyperkalemia) [48]. Exact timing of initiation of RRT, similar to the general critically ill population, is controversial [49].

### 12.1.13 Extracorporeal Liver Support

Extracorporeal albumin dialysis technologies utilize albumin as a binding and scavenging molecule in the treatment of HRS. Albumin dialysis is based upon dialyzing blood against

an albumin containing solution across a highly permeable high-flux membrane. The blood-bound toxins are cleared by diffusion and taken up by the binding sites of the albumin dialysate.

**MARS** (molecular adsorbent recirculating system) consists of a blood circuit, an albumin circuit and a classic renal circuit. Blood is dialyzed across an albumin impregnated high-flux dialysis membrane; 600 mL of 20% human albumin in the albumin circuit acts as the dialysate. Albumin bound toxins in blood are released to the membrane. In a controlled pilot study, *Mitzner et al.* reported 13 patients with decompensated cirrhosis and type 1 HRS; 8 were treated with MARS and 5 received standard medical therapy [50]. They showed a 37.5% absolute survival benefit at day 7 vs. 0% in controls. A significant decrease in creatinine and bilirubin was also noted in the MARS group. A more recent multicenter study (RELIEF trial) by Banares et al. failed to show a mortality benefit in ACLF patients treated with MARS with a 28-day survival of 60% in both MARS and SMT groups despite biochemical improvement. This study may have been confounded by indication (transplant and non-transplant candidates) [51]. **Prometheus** (fractionated plasma separation and adsorption) differs from the other technologies in that the patient's plasma is separated across a membrane and then is run over adsorptive columns. In an uncontrolled study reported Prometheus use in 10 patients with HRS who underwent 2 consecutive Prometheus treatments [52]. A statistically significant decrease in creatinine and blood urea nitrogen levels and improvement in arterial blood pH was observed. More recent multicenter study (HELIOS) failed to show a mortality benefit in ACLF patients treated with Prometheus with a 28-day survival of 65% in both Prometheus and SMT groups despite biochemical improvement [53]. Like RELIEF, this study also was confounded by indication.

### 12.1.14 Treatment: Other Causes of AKI

Early treatment of AKI in cirrhosis is important. Multiple therapies may be initiated prior to an unequivocal diagnosis of the exact cause of AKI. Nephrotoxins such as NSAIDs and ACEIs should be discontinued in patients taking them. Patients on diuretic therapy who develop AKI should stop loop and potassium-sparing diuretics. In patients with large volume ascites, paracentesis may still be warranted to reduce the risk of an abdominal compartment syndrome and improve venous return to the right atrium but intravenous albumin at 8 g/L is required to maintain intravascular volume. In the patient who is hypotensive (mean arterial pressure < 65 mm Hg), it may be reasonable to consider vasoconstrictor therapy and volume resuscitation unless there is evidence of volume overload (e.g. echocardiography). Intravascular depletion can be treated with albumin or crystalloid depend-

ing on biochemical factors. In the setting of gastrointestinal bleeding, packed red blood cell transfusion below 7 g/dL has been shown to be non-inferior and potentially beneficial over a more liberal transfusion strategy [54].

### 12.1.15 Natural History of AKI: Pre and Post Transplant

The importance of novel methods of identifying the etiology of AKI in cirrhosis is important as the potential for renal recovery is etiology dependent [55]. Pre-renal azotemia (i.e., diuretics, diarrhea) is usually reversible following discontinuation of the precipitating cause [56]. The severity of AKI associated with bacterial infection depends on the resolution of the infection [57]. Etiology of AKI also has a significant impact on patient and renal outcomes post LT. A recent study from Nadim et al. revealed that patient survival and renal outcomes 1 and 5 years after LT were significantly worse for those with ATN [58].

Intraoperative RRT in critically ill cirrhotic patients undergoing LT has been shown to be feasible with good patient and renal outcomes [23].

While some centers use duration of RRT (4–8 weeks) and GFR have been traditionally used to determine the need for simultaneous liver kidney (SLK) transplants, evidence based guidelines for SLK are lacking [58]. Further investigations, particularly focusing on novel renal plasma protein biomarkers may provide further information on prognostication of potential post-LT renal recovery (along with etiology of AKI) prior to making a decision to proceed with SLK transplantation [36].

### Conclusions

Acute kidney injury causes significant morbidity in cirrhotic patients. Evaluation of renal dysfunction in patients with cirrhosis remains a critically important and challenging problem. Current diagnostic criteria are based on serum creatinine, which has limitations in extrapolating glomerular filtration rate in cirrhotics. New diagnostic criteria (KDIGO, RIFLE, AKIN) have been integrated with traditional approaches (ICA/HRS/AKI) to potentially identify AKI earlier and improve outcomes. Etiology of AKI has a significant impact on potential of renal recovery. Further work on urinary tubular biomarkers is required to differentiate structural causes of AKI vs. hepatorenal syndrome (HRS-AKI). Conventional therapies for HRS include vasoconstrictor agents and albumin although in severe cases where mortality is high, liver transplant is the only effective treatment. Novel renal plasma protein biomarkers may in the future provide further information on the potential of renal recovery post-LT (along with etiology) and potentially impact the decision to allocate a SLK.

**Conflict of Interest** All authors: None.

## References

1. Sanyal AJ, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology*. 2008;134:1360–8.
2. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. *Gut*. 2013;62:131–7.
3. Barreto R, et al. Type-1 hepatorenal syndrome associated with infections in cirrhosis: natural history, outcome of kidney function, and survival hepatology. *Hepatology*. 2014;59:1505–13.
4. Piano S, et al. Evaluation of the acute kidney injury network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol*. 2013;59:482–9.
5. Wong F, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology*. 2013;145:1280–8. E1
6. Adebayo D, et al. Renal dysfunction in cirrhosis is not just a vaso-motor nephropathy. *Kidney Int*. 2015;87:509–15.
7. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–90.
8. Stadlbauer V, et al. Relationship between activation of the sympathetic nervous system and renal blood flow autoregulation in cirrhosis. *Gastroenterology*. 2008;134:111–9.
9. Salerno F, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310–8.
10. Moreau R, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology*. 2002;122:923–30.
11. Warner NS, et al. Acute kidney injury and chronic kidney disease in hospitalized patients with cirrhosis. *J Investig Med*. 2011;59:1244–51.
12. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology*. 2008;48:2064–77.
13. Wong F, et al. Working party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*. 2011;60:702–9.
14. Martin PY, et al. Nitric oxide synthase (Nos) inhibition for one week improves renal sodium and water excretion in cirrhotic rats with ascites. *J Clin Invest*. 1998;101:235–42.
15. Gines P, et al. Hepatorenal syndrome. *Lancet*. 2003;362:1819–27.
16. Lee HT, et al. Acute kidney injury after hepatic ischemia and reperfusion injury in mice. *Lab Invest*. 2009;89:196–208.
17. Park SW, et al. Paneth cell-derived interleukin-17a causes multi-organ dysfunction after hepatic ischemia and reperfusion injury. *Hepatology*. 2011;53:1662–75.
18. Proulx NL, et al. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. *Nephrol Dial Transplant*. 2005;20:1617–22.
19. Francoz C, et al. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol*. 2010;52:605–13.
20. Levey AS, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of diet in renal disease study group. *J Am Soc Nephrol*. 1999;10:2426–39.
21. Francoz C, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. *Liver Transpl*. 2010;16:1169–77.
22. Gonwa TA, et al. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl*. 2004;10:301–9.
23. Francoz C, et al. Glomerular filtration rate equations for liver-kidney transplantation in patients with cirrhosis: validation of current recommendations. *Hepatology*. 2014;59:1514–21.
24. Gerbes AL, et al. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. *Gut*. 2002;50:106–10.
25. Davenport A, et al. Pitfalls in assessing renal function in patients with cirrhosis – potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant*. 2011;26:2735–42.
26. Mindikoglu AL, et al. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology*. 2014;59:1532–42.
27. De Souza V, et al. Creatinine-versus cystatin C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. *Hepatology*. 2014;59:1522–31.
28. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. *Intensive Care Med*. 2004;30:33–7.
29. Mehta RL, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
30. Kdigo. Kidney Disease: Improving Global Outcomes (KDIGO) Acute kidney injury work group kdigo clinical practice guideline for acute kidney injury. *Kidney Int* 2012;Suppl.:1–138.
31. Nadim MK, et al. Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2012;16:R23.
32. Belcher JM, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology*. 2013;57:753–62.
33. De Carvalho JR, et al. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J Clin Gastroenterol*. 2012;46:E21–6.
34. Belcher JM, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology*. 2014;60:622–32.
35. Altamirano J, et al. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. *Clin Gastroenterol Hepatol*. 2012;10:65–71. E3
36. Levitsky J, et al. Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. *Hepatology*. 2014;60:2017–26.
37. Fernandez J, et al. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol*. 2004;41:384–90.
38. Sort P, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–9.
39. Martin-Llahi M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology*. 2008;134:1352–9.
40. Gluud LL, et al. Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev*. 2012;9:CD005162.
41. Angeli P, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. *Gut*. 2014. <https://doi.org/10.1136/Gutjnl-2014-307526>.
42. Alessandria C, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol*. 2007;47:499–505.
43. Sharma P, et al. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. *Am J Gastroenterol*. 2008;103:1689–97.



44. Nassar Junior AP, et al. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One*. 2014;9:E107466.
45. Skagen C, et al. Combination treatment with octreotide, midodrine, and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. *J Clin Gastroenterol*. 2009;43:680–5.
46. Guevara M, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology*. 1998;28:416–22.
47. Brensing KA, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut*. 2000;47:288–95.
48. Keller F, et al. Risk factors and outcome of 107 patients with decompensated liver disease and acute renal failure (including 26 patients with hepatorenal syndrome): the role of hemodialysis. *Ren Fail*. 1995;17:135–46.
49. Karvellas CJ, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2011;15:R72.
50. Mitzner SR, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis mars: results of a prospective, randomized, controlled clinical trial. *Liver Transpl*. 2000;6:277–86.
51. Banares R, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the relief trial. *Hepatology*. 2013;57:1153–62.
52. Rifai K, et al. The prometheus device for extracorporeal support of combined liver and renal failure. *Blood Purif*. 2005;23:298–302.
53. Kribben A, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology*. 2012;142:782–9.E3.
54. Villanueva C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368:11–21.
55. Arroyo V. Acute kidney injury (AKI) in cirrhosis: should we change current definition and diagnostic criteria of renal failure in cirrhosis? *J Hepatol*. 2013;59:415–7.
56. Martin-Llahi M, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology*. 2011;140:488–96. E4
57. Follo A, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology*. 1994;20:1495–501.
58. Nadim MK, et al. Impact of the etiology of acute kidney injury on outcomes following liver transplantation: acute tubular necrosis versus hepatorenal syndrome. *Liver Transpl*. 2012;18:539–48.
59. Bellomo R, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care*. 2004;8:R204–12.
60. Angeli P, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the international club of ascites. *J Hepatol*. 2015. <https://doi.org/10.1016/j.jhep.2014.12.029>.

R. Todd Stravitz

**Abstract**

Patients with liver disease have long been considered at risk for bleeding complications. Although bleeding in patients with cirrhosis occurs frequently on the basis of portal hypertension, evidence accumulated over the last 10 years suggests that the underlying state of hemostasis in patients with cirrhosis and acute liver failure appears to be “re-balanced,” such that redundant mechanisms exist to compensate for deficient pro-coagulant, liver-derived factors. Recent clinical and *in vitro* research has demonstrated that stable patients with acute and chronic liver failure actually exist in a relative hypercoagulable state, which may propagate the progression of liver disease itself as well as cause systemic thrombotic complications. Surely, treating such patients with blood and blood products has the potential to exacerbate the hypercoagulable state and cause harm. The following will summarize much of the background to the new concept of re-balanced hemostasis in patients with cirrhosis and acute liver failure, and suggest therapeutic options other than repleting blood products to achieve a “goal,” the often unattainable normalization of standard coagulation laboratories.

**Keywords**

Hemostasis • Cirrhosis • Acute liver failure • Bleeding • Thrombosis • Coagulopathy

**Abbreviations**

ACLF	acute-on-chronic liver failure	NASH	non-alcoholic steatohepatitis
ADAMTS-13	a disintegrin and metalloprotease with thrombospondin type-1 motifs 13	PS	phosphatidylserine
ALF	acute liver failure	PVT	portal vein thrombosis
AT	antithrombin	RBC	red blood cells
HCC	hepatocellular carcinoma	rFVIIa	recombinant activated factor VII
ICP	intracranial monitor	RRT	renal replacement therapy
INR	International Normalized Ratio of the pro-thrombin time	SIRS	systemic inflammatory response syndrome
LMWH	low molecular weight heparin	SMV	superior mesenteric vein
MOSF	multiorgan system failure	TEG	thromboelastography
		TF	tissue factor
		TM	thrombomodulin
		VTE	venous thromboembolism
		vWF	vonWillebrand factor

R.T. Stravitz, M.D.  
 Hume-Lee Transplant Center of Virginia Commonwealth  
 University, Richmond, VA, USA  
 e-mail: [richard.stravitz@vcuhealth.org](mailto:richard.stravitz@vcuhealth.org)

### Learning Objectives

1. To review current concepts of the state of global hemostasis in patients with cirrhosis and acute liver failure;
2. To identify mechanisms of compensation for deficient liver-derived, pro-coagulant factors and thrombocytopenia;
3. To examine the state of re-balanced hemostasis, which may, in fact, be tipped toward thrombosis;
4. To offer therapeutic options for administering pro-coagulant factor and red blood cell transfusions in patients with acute and chronic liver failure; and,
5. To identify major deficiencies that persist between the laboratory science which led to the concept of re-balanced hemostasis in liver disease, and the clinical application of these new concepts.

## 13.1 Introduction

Clinicians often regard patients with advanced liver disease as prone to bleeding. While accurate when considering portal hypertensive bleeding, this perception has been recently challenged as inaccurate. There are 3 potential reasons for the misconception of a bleeding diathesis: [1] patients with liver disease often have laboratories that suggest insufficient hemostasis (low platelet count and high International Normalized Ratio [INR] of the prothrombin time), [2] clinicians may not appreciate the difference in pathogenesis between portal hypertensive and non-portal hypertensive bleeding, and, [3] clinicians are wary of causing harm, particularly after an invasive procedure. The following discussion will explore recent data which redefine the magnitude of the bleeding diathesis in patients with advanced cirrhosis and acute liver failure (ALF), and will explore mechanisms of “re-balanced hemostasis,” a relatively new concept in which patients re-establish a neutral state of pro- and anti-hemostatic drivers by compensatory mechanisms [1]. Bleeding compli-

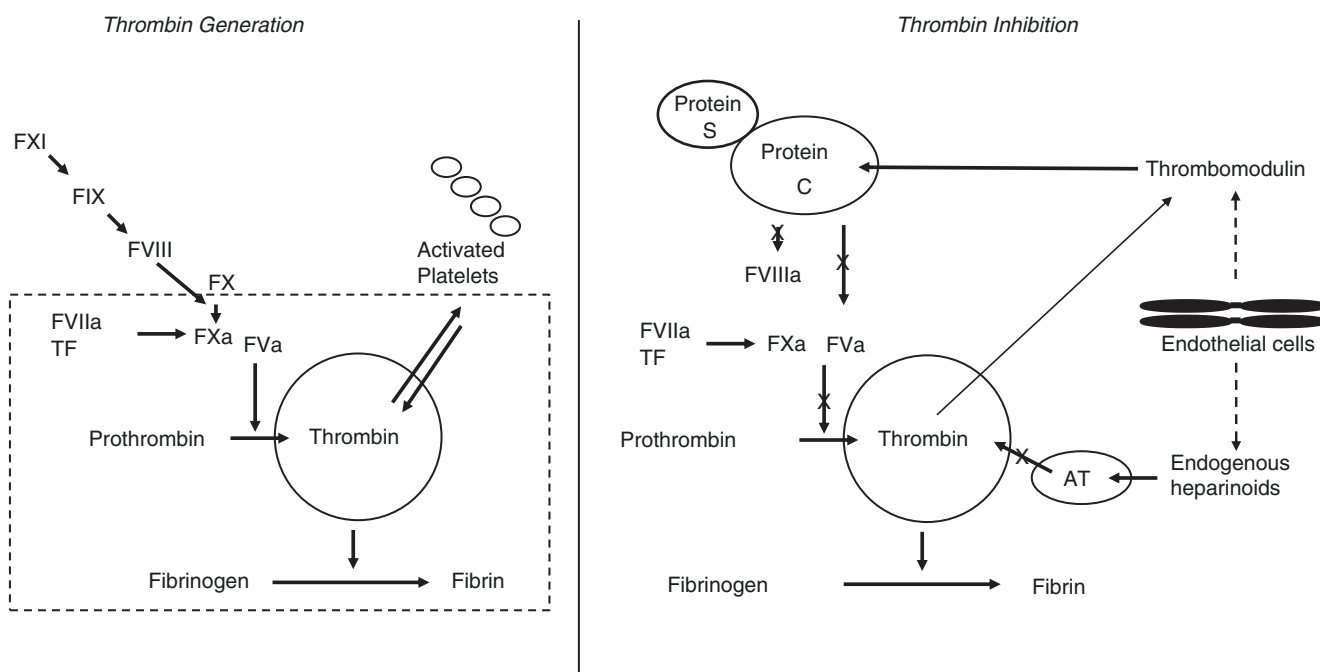
cations of portal hypertension will not be considered, since they occur as a consequence of hydrostatic pressure and wall tension within blood vessels [2] rather than defective hemostasis.

The perception of a bleeding diathesis may be fueled by different clinical features of patients with cirrhosis or ALF (Fig. 13.1). Patients with cirrhosis have varying degrees of portal hypertension, which results in platelet sequestration within the spleen, and thrombocytopenia, which can be severe. In contrast, patients with ALF have modest (if any) portal hypertension, and thereby more moderate thrombocytopenia due to a different mechanism [3]. Instead, clinicians consider patients with ALF at high risk of bleeding complications because of the often dramatically increased INR, the severity of which is relatively modest in cirrhosis. Acute and chronic liver failure also differ in the severity of the systemic inflammatory response syndrome (SIRS), highly activated in patients with ALF, and less so in patients with stable cirrhosis. As will be discussed below, the SIRS is a prominent feature of the ALF syndrome [4] which activates compensatory mechanisms to re-balance defects in hemostasis.

The traditional reliance on the INR as a marker of increased bleeding risk in patients with liver disease is a misconception [5]. The INR was designed to measure the efficacy of warfarin, not estimate bleeding risk; no correlation exists between the INR and post-procedural bleeding in patients with liver disease [6]. Simplistically, the INR assays measures only a limited portion of overall hemostasis, the extrinsic and final common pathways of the coagulation cascade (Fig. 13.2, dotted box), and does not account for the contribution of the intrinsic coagulation cascade and activated platelets, or the anti-hemostatic pathways (mediated by protein C/S and antithrombin [AT]), to thrombin generation. Thus, although the INR detects deficiencies in liver-derived, pro-hemostatic factors, it provides insufficient and unreliable information to estimate bleeding risk after an invasive procedure.

**Fig. 13.1** Clinical features of cirrhosis and acute liver failure contributing to the perception of bleeding risk. The relative severity of the indicated clinical feature of cirrhosis and acute liver failure is depicted as: +++ Major feature; +/++ Mild-moderate feature; -/+ Insignificant feature

Clinical Feature	Cirrhosis	Acute Liver Failure
Portal Hypertension	+++	-/+
Thrombocytopenia	+++	+ / ++
Synthetic Failure (high INR)	+ / ++	+++
Systemic Inflammation	+ / ++	+++



**Fig. 13.2** Simplified representation of pathways of thrombin generation and inhibition, yielding fibrin. Thrombin is generated by the sequential activation of liver-derived pro-hemostatic factors in the traditional coagulation cascades, but also by activated platelets. The exception to this rule is factor VIII, which is derived from endothelial cells, and is increased in both cirrhosis and acute liver failure. Thrombin generation is limited by liver-derived anticoagulant proteins C, S, and antithrombin (AT). The protein C/S complex serves as an anticoagulant factor by inactivating factors Va and VIIIa. Endothelial cells also pro-

duce two anticoagulant factors, thrombomodulin, which is required for full activation of protein C, and endogenous heparinoids, which activate AT. In the absence of thrombomodulin *in vitro*, thrombin generation is therefore overestimated because protein C is not fully activated. The dotted box within the thrombin generation scheme represents the limitation of the INR as a measure of hemostasis, as it includes contributions only from the factor VII-tissue factor (TF) pathway, and the final common pathway of the coagulation cascades

Some professional societies have made recommendations regarding correction of the INR and platelet count before invasive procedures. The Society of Interventional Radiologists has recommended correction of the INR with plasma to  $<1.5$  and transfusion of platelets when  $<50 \times 10^9/L$  before invasive procedures with moderate bleeding risk such as trans-jugular liver biopsy [7]. The same guidelines do not recommend a goal for transfusion of platelets, however, and were based upon expert consensus opinion rather than evidence that transfusions decrease bleeding complications. In fact, these guidelines state that there are no data to support nor refute their recommendations. In contrast, Practice Guidelines of the American Association for the Study of Liver Diseases regarding liver biopsy neither specify a threshold, nor a goal INR or platelet count, for transfusions [8], acknowledging insufficient evidence to make such recommendations. There are many reasons to avoid transfusions of plasma and platelets, including transfusion-related lung injury, volume overload, expense, thrombosis, and the rare transmission of hepatitis or human immunodeficiency viruses. In addition, increasing experimental evidence suggests that patients with acute and chronic liver disease are actually hypercoagulable [9, 10],

raising the question of whether such transfusions may cause harm by exacerbating the hypercoagulable state. Clinicians must also recognize that a goal INR may not be achievable with plasma transfusion in patients with ALF, and the survival of platelets in patients with cirrhosis and hypersplenism is short. Thus, the practice of transfusion to correct a high INR or thrombocytopenia in a patient with severe acute or chronic liver disease is unproven and potentially harmful.

## 13.2 Chronic Liver Disease

### 13.2.1 Cirrhosis as a Re-balanced State of Hemostasis

Apart from the effects of portal hypertension on the risk of gastrointestinal bleeding, Tripodi et al., have made a persuasive argument that patients with advanced cirrhosis may not have a bleeding diathesis [1]. The arguments include the observation that patients with cirrhosis do not spontaneously bleed similar to those with hereditary or acquired coagulation factor deficiencies; for example, they do not present

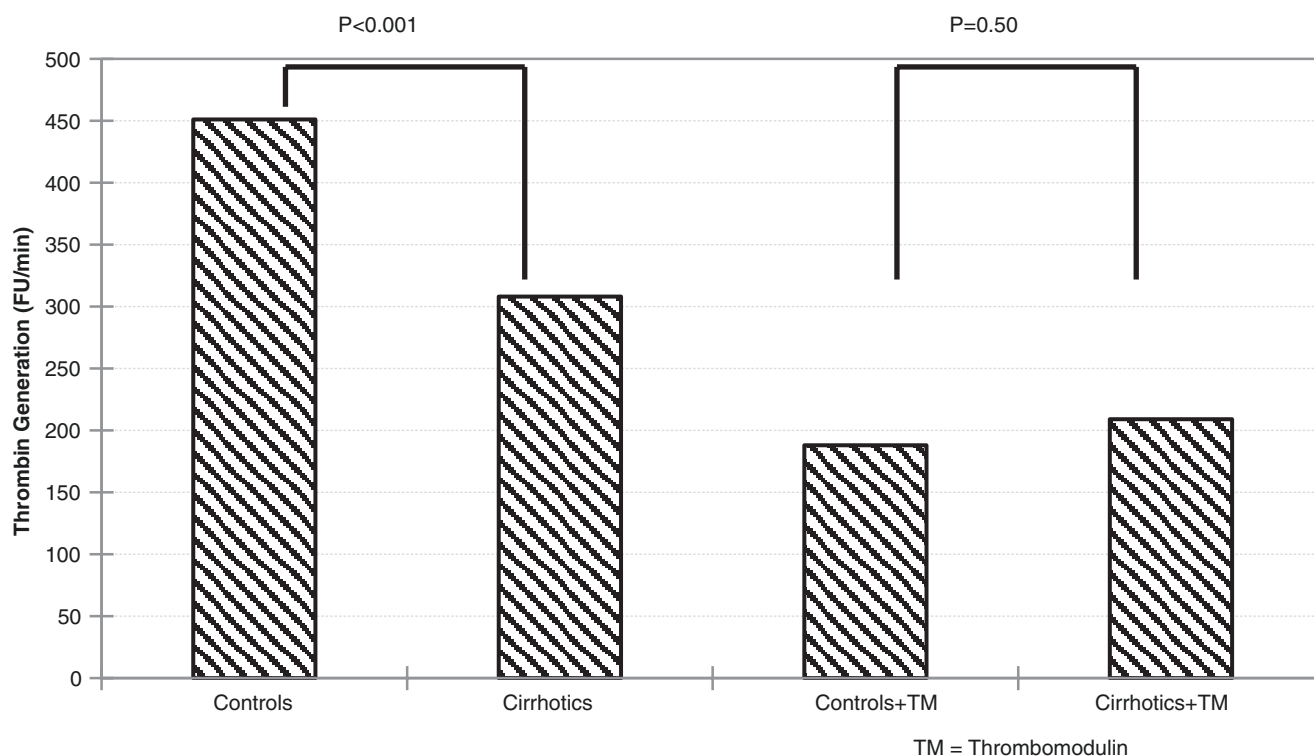


with hemarthroses. The use of recombinant activated factor VII (rFVIIa) to treat esophageal variceal bleeding or prevent rebleeding also provide evidence against the contribution of abnormal hemostasis to variceal bleeding, as these studies showed no apparent benefit [11, 12].

The seminal experimental evidence documenting the concept of “rebalanced hemostasis” was provided by Tripodi and associates in 2005 [13], who showed that thrombin generation in patients with cirrhosis was similar to that in normal healthy controls (Fig. 13.3). Although thrombin generation in cirrhotics was initially found to be lower than controls presumably due to lower levels of pro-coagulant factors synthesized by liver failure (2 left bars), the same experiments in the presence of thrombomodulin (TM), an endogenous activator of protein C derived from endothelial cells, showed that thrombin generation in cirrhotics was not significantly lower than controls (2 right bars). These experiments provided the first evidence of “re-balanced” hemostasis, in which pro- and anti-coagulant, liver-derived coagulation factors decrease in parallel in patients with cirrhosis. Thus, thrombin generation in cirrhotics is similar to normal healthy controls, but only if

the assay conditions account for missing endothelial proteins to activate protein C (i.e., by the addition of TM). In addition, other endothelial cell-derived, pro-coagulant factors are increased in patients with cirrhosis to compensate for deficient liver-derived proteins, such as factor VIII [9].

A second critical set of experiments has provided a potentially important threshold for the platelet count, below which clinicians might be wary of procedure-related bleeding complications in patients with cirrhosis [14]. Recognizing the importance of platelets to thrombin generation, Tripodi et al., performed thrombin generation assays in plasma from normal healthy controls containing normal platelet counts. Thrombin generation in 90% of normal healthy controls (with a median platelet count of  $198 \times 10^9/L$ ) was  $\geq 875$  nmol/L. Defining this level of thrombin generation as “normal,” the investigators repeated the experiments using plasma from patients with cirrhosis into which platelets were added back to the reaction mixture in increasing numbers, and found that a platelet count of  $56 \times 10^9/L$  was adequate to generate  $\geq 875$  nmol/L thrombin. These observations suggest that  $\sim 60 \times 10^9/L$  may



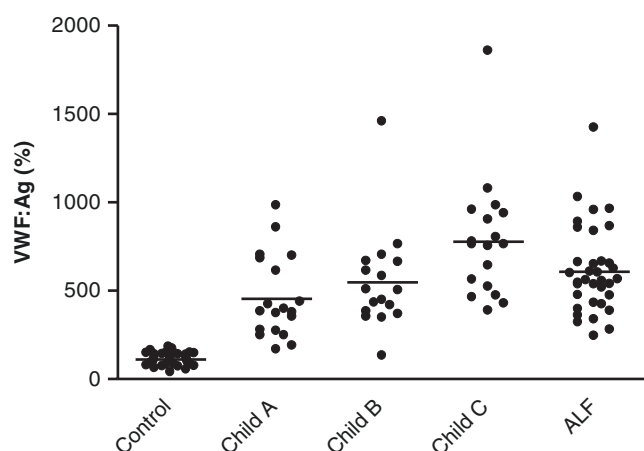
**Fig. 13.3** Thrombin generation in patients with cirrhosis and normal healthy controls. The two bars on the left depict thrombin generation in patients with cirrhosis and healthy controls, and show that cirrhotics generate less thrombin than controls, presumably due to decreased synthesis of pro-hemostatic coagulation factors (most importantly, factors V and VII) in the former. The experiments depicted in the two bars on the right included thrombomodulin (TM) in the reaction mixture, an

endogenous endothelial activator of the anticoagulant, protein C. Thus, since protein C and pro-hemostatic factors are liver-derived and are proportionally decreased in patients with liver failure, thrombin generation remains “re-balanced,” as long as TM is added to the reaction mixture to activate protein C. (Adapted from Tripodi, et al. *Hepatology*. 2005; 41: 553) [13]

serve as a guideline for platelet transfusion prior to invasive procedures in patients with cirrhosis, and also possibly a goal of transfusion. Obviously, clinical correlation is urgently needed.

In addition to their function as activators of thrombin, platelets also serve to adhere to endothelial defects in primary hemostasis *via* the endothelial-derived protein, von Willebrand factor (vWF). Although patients with cirrhosis and portal hypertension typically have thrombocytopenia, they also have high levels of vWF in proportion to the severity of liver failure, which can increase platelet adherence and compensate for numerical deficiency (Fig. 13.4) [15]. Regulation of the size of vWF multimers by deficiency of the liver-derived protease, ADAMTS-13, may also compensate for thrombocytopenia. ADAMTS-13 cleaves vWF into smaller multimers with lower capacity of platelet-endothelial binding; thus, deficient ADAMTS-13 may yield larger vWF multimers with increased platelet-endothelial binding capacity [16].

Fibrinolysis in patients with cirrhosis also exhibits a state of partial compensation. Deficiency of liver-derived plasminogen is thereby rebalanced by deficiency in anti-fibrinolytic proteins  $\alpha$ 2-antiplasmin and thrombin-activatable fibrinolysis inhibitor, and by high levels of tissue plasminogen activator. In summary, the 3 phases of hemostasis exist in a state of re-balance in patients with cirrhosis, such that deficiencies of liver-derived pro-coagulant factors are compensated by deficiencies in liver-derived anti-coagulant factors,



**Fig. 13.4** VonWillebrand antigen levels in plasma from patients with cirrhosis and acute liver failure. A major compensatory mechanism is likely to exist in both cirrhosis and acute liver failure (ALF) in that endothelial secretion of vonWillebrand factor (vWF) increases as a function of the severity of liver failure. The increase in vWF was significantly higher in patients with cirrhosis and ALF compared to normal healthy controls, and each successive Child class. (Adapted from Lisman, et al., *Hepatology*. 2006; 44: 53 and Hugenholtz, et al., *Hepatology*. 2013; 58: 752) [15, 66]

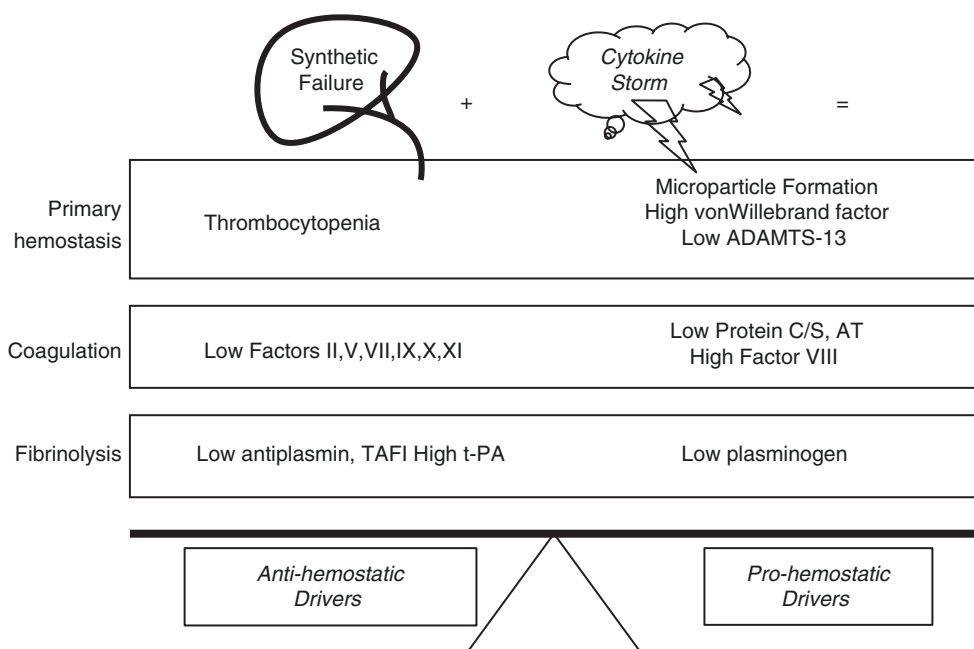
as well as increased levels of pro-coagulant endothelial cell-derived factors (e.g., vWF, factor VIII, tPA) (Fig. 13.5).

### 13.2.2 Management: Blood and Blood Product Transfusions in Cirrhosis

Unfortunately, the concept of re-balanced hemostasis in cirrhosis has not been rigorously tested in clinical situations; there are no randomized, prospective studies which document the safety of *not* administering plasma or platelet transfusions before invasive procedures. However, clinical correlations exist which support sparing many patients blood product transfusions. For example, a series from an intensive care liver unit described 658 central venous cannulations in 283 patients with INR  $\geq 1.5$  and/or platelet count  $\leq 150 \times 10^9/L$  without routine plasma or platelet transfusions, resulting in only 1 serious bleeding complication [17]. Even liver transplantation in decompensated cirrhotics is often accomplished without the need for blood or blood product transfusion in response to improvements in surgical technique and cell-saver technology [18].

An attempt to systematically explore the rational administration of blood products before invasive procedures in patients with cirrhosis was recently reported in 60 patients with “significant coagulopathy,” defined as an INR  $>1.8$  and/or platelet count  $<50 \times 10^9/L$  [19]. Patients randomized to the standard of care group received plasma at the dose of 10 mL/kg of ideal body weight for INR  $>1.8$  and/or platelets in the amount of 1 unit if the platelet count were below  $50 \times 10^9/L$ . Patients randomized to the study group only received plasma or platelet transfusions based upon specific (and largely arbitrary) abnormal thromboelastography (TEG) parameters [20]. As shown in Fig. 13.6, only 17% of patients in the TEG group received a blood product transfusion vs. 100% of the standard-of-care group (by definition), with no difference in the rare occurrence of procedure-related bleeding complications.

The transfusion of red blood cells (RBC) in patients with cirrhosis has been recommended when the hemoglobin  $<8$  g/dl [21] with the caveat that post-transfusion hemoglobin should not exceed 8 g/dl due to rebound portal hypertension caused by over-transfusion, with increased re-bleeding and mortality in experimental models [22]. The same caution regarding increasing portal pressures with plasma infusion to correct the INR should also be recognized [23]. However, RBC’s serve an important function in physically occupying space within blood vessels, and profound RBC deficiency may thereby decrease platelet-endothelial approximation. In a randomized, controlled study of 921 patients with severe acute upper gastrointestinal hemorrhage (31% of whom had cirrhosis and ~25% bleeding from varices), half were resuscitated by RBC with a restrictive



**Fig. 13.5** The three phases of hemostasis in patients with cirrhosis and acute liver failure exist in a state of "re-balance." Primary hemostasis in both conditions is defective due to thrombocytopenia, but is compensated for by platelet microparticle formation (for ALF), and by increased vWF synthesis by endothelial cells. Deficiency of ADAMTS-13, a liver-derived protease, may also increase vWF multimer size and thus its ability to promote the adherence of platelets to endothelial defects. Defects in secondary hemostasis, in which liver-derived, pro-hemostatic factors are decreased because of liver failure,

are compensated for by deficiencies of the liver-derived, anti-hemostatic proteins, protein C/S and antithrombin (AT), and by high levels of endothelial cell-derived factor VIII. Finally, fibrinolysis is defective because of low liver-derived plasminogen, but compensated for by low levels of anti-fibrinolytic, liver-derived proteins such as  $\alpha 2$ -antiplasmin and high levels of endothelial cell-derived tissue plasminogen activator (tPA). (Adapted from Tripodi and Mannucci. *New Engl J Med.* 2011; 365: 147) [1]

Product/ Outcome	SOC (N=30)	TEG (N=30)	P
Plasma	53%	0	<.0001
Platelets	33%	6.7%	.021
Overall Transfusion	100%	16.7%	<.0001
Bleeding Complication	3.3%	0	.313

**Fig. 13.6** Thromboelastography-guided blood product use before invasive procedures in cirrhotics with severe coagulopathy: Results of a randomized, controlled trial. Results of a prospective study of 60 patients with cirrhosis and "severe coagulopathy," defined as INR >1.8 and/or platelet count <50  $\times 10^9/L$ , randomized to standard-of-care (SOC) administration of plasma and/or platelets, or to transfusion guided by abnormal thromboelastography (TEG) parameters prior to an invasive procedure. (Adapted from De Pietri, et al. *Hepatology.* 2016; 63: 566) [19]

strategy (hemoglobin threshold for transfusion 7 g/dl with a target range for the post-transfusion hemoglobin 7–9 g/dl) and the other half were resuscitated with a liberal strategy (hemoglobin threshold for transfusion 9 g/dl with a target

range for the post-transfusion hemoglobin level of 9–11 g/dl) [24]. As shown in Fig. 13.7, patients managed under the restrictive strategy had lower death and re-bleeding rates, and shorter hospital stays; in particular, variceal re-bleeding was decreased by 50%. Accordingly, RBC transfusion constitutes an important management adjunct to maintain or restore re-balanced hemostasis in patients with cirrhosis, but should be administered conservatively to avoid exacerbating portal hypertension.

### 13.2.3 Cirrhosis as a Hypercoagulable State

In contrast to the perception of a bleeding tendency, thrombosis has become increasingly recognized as a major clinical problem in patients with cirrhosis, not only in peripheral vascular beds but also within hepatic vasculature itself. As a hypercoagulable state within the liver, thrombosis may contribute to the pathogenesis of cirrhosis and portal hypertension. Wanless et al. [25] graded portal and hepatic venous micro-obstructive lesions in explanted livers and found a direct correlation with focal parenchymal extinction within the same vascular distribution. These seminal observations suggested that thrombosis of portal and hepatic vessels prop-

Endpoint	Restrictive Strategy N=444	Liberal Strategy N=445	HR	P
Death	5%	9%	0.55	0.02
Rebleeding (all patients)	10%	16%	0.62	0.01
Variceal rebleeding (25%)	11%	22%	0.50	0.05
Hospital days	9.6 ± 8.7	11.5 ± 12.8	-	0.01
Any complications	40%	48%	0.73	0.02

**Fig. 13.7** Outcomes after “restrictive” vs. “liberal” red blood cell transfusion strategies in resuscitating patients after severe upper gastrointestinal bleeding. A randomized, controlled study of 921 patients with severe acute upper gastrointestinal hemorrhage (31% of whom had cirrhosis and ~25% bled from varices). Half of patients were resuscitated by RBC with a restrictive strategy (hemoglobin threshold for transfu-

sion 7 g/dl with a target range for the post-transfusion hemoglobin 7–9 g/dl) and the other half were resuscitated with a liberal strategy (hemoglobin threshold for transfusion 9 g/dl with a target range for the post-transfusion hemoglobin level of 9–11 g/dl). (Adapted from Villaneuva, et al. *New Engl J Med.* 2013; 368: 11) [24]

agated parenchymal collapse, worsened portal hypertension, and increased the risk of variceal bleeding.

Several clinical observations also support the presence of a hypercoagulable state in patients with cirrhosis. The incidence of venous thromboembolism (VTE) in patients with cirrhosis admitted to one tertiary care hospital was 0.5% despite a mean INR of approximately 1.5 [26]. Another case-control study showed that the incidence of VTE was higher in 963 cirrhotics admitted to the hospital compared to 12,405 non-cirrhotic controls (1.8 vs. 0.9%, respectively;  $P = 0.007$ ) [27]. Although there was no relationship of the INR to the increased risk of VTE in study participants, an inverse relationship of VTE with serum albumin was observed, suggesting a possible relationship with deficiencies of endogenous anticoagulant proteins. In a population-based study, unprovoked VTE was approximately 2-fold more common in patients with cirrhosis than controls [28]. Finally, the thrombosis of continuous renal replacement therapy (RRT) circuits in patients with liver failure was more rapid and more common than in controls, and could be delayed by anticoagulation without an obvious increase in bleeding complications [29]. Thus, the concept of “autoanticoagulation,” the notion that patients with cirrhosis are protected *de facto* from VTE by virtue of elevated INR, has been strongly refuted.

Studies to define the mechanisms by which some patients with cirrhosis have a hypercoagulable state are on-going. According to the study noted above, Tripodi et al. [13] first noted that the addition of TM decreased thrombin generation (by activating protein C) less effectively in patients with cir-

rhosis than normal healthy controls (Fig. 13.2), and hypothesized that this difference represented the basis of a hypercoagulable state. Further studies by the same laboratory noted increased factor VIII levels and reduced protein C and AT levels in patients with cirrhosis compared to controls as a function of the severity of cirrhosis and liver failure (Child-Pugh Score) [9]. Thus, the ratios of pro- and anti-coagulants (factor VIII/protein C and factor VIII/AT) increased proportionally from compensated to severely decompensated cirrhosis, creating an imbalance of hemostasis favoring thrombosis.

Subsequent studies have documented that certain etiologies of chronic liver disease may be associated with a greater risk of thrombosis of splanchnic and peripheral vascular beds than others. Using TEG, a test of global hemostasis in whole blood [20], Ben-Ari et al. [30] found that patients with primary biliary cirrhosis and primary sclerosing cholangitis were more likely to have a hypercoagulable state than patients with other causes of liver diseases. More recent attention has attempted to explain the observation that patients with non-alcoholic steatohepatitis (NASH) appear particularly prone to develop portal vein and non-splanchnic thrombosis than other liver diseases [31]. Analysis of the United Network for Organ Sharing database of liver transplants in the US showed that patients that NASH was an independent predictor of portal vein thrombosis (PVT) [32]. The mechanisms by which NASH increases the risk of PVT are not well established [33], but the pro-coagulant imbalance (factor VIII/protein C ratio) described above has been shown to increase as a func-

tion of the severity of the metabolic syndrome and NASH-induced liver disease, and was highest in patients with NASH cirrhosis [34]. Increased levels of plasminogen activator inhibitor-1, an inhibitor of fibrinolysis, have also been described in patients with metabolic syndrome and NASH [35], and may promote systemic atherogenesis as well as fibrogenesis and liver disease progression.

### 13.2.4 Management of the Hypercoagulable State in Patients with Cirrhosis

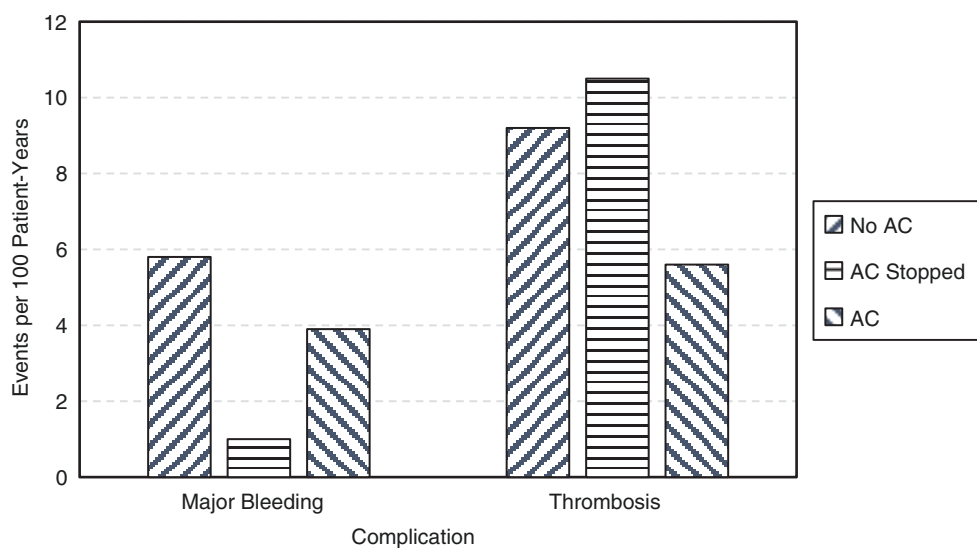
Non-malignant (non-HCC-related) PVT occurs in up to 25% of patients with cirrhosis awaiting liver transplantation, as a result of the relative hypercoagulable state discussed above as well as pooling and stagnant flow and local endothelial dysfunction within the portal vein [36]. Cirrhosis is the most important risk factor for PVT [37]. Often, PVT is discovered as an incidental finding at the time of ultrasound surveillance for HCC, with a 5-year cumulative incidence of 10.7% [38]. The risk of PVT reflects the severity of underlying cirrhosis and its incidence increases with decompensation. Although PVT does not appear to be responsible for the progression of cirrhosis *per se* [38], its occurrence is associated with acute decompensation, variceal bleeding, and increased mortality [39]. Non-occlusive is much more common than occlusive PVT, and the prevalence of the former varies with time due to spontaneous recanalization in up to 70%. The development of PVT is frequently subacute and subclinical, but acute propagation into the superior mesenteric vein (SMV) can lead to gut ischemia, gastrointestinal bleeding, and bowel infarction. Propagation into the SMV may also render a patient un-transplantable. Therefore, prevention of PVT is generally considered desirable.

A small but seminal study by Villa et al. [40] randomized 70 patients with Child's B/C cirrhosis to enoxaparin

(4000 IU/d) or placebo for 48 weeks to determine whether PVT could be safely prevented. Study participants with evidence of PVT on computerized tomography-angiography were excluded; high-risk esophageal varices required prophylactic band ligation prior to randomization. The 2-year prevention of porto-mesenteric venous thrombosis detected by 3-month ultrasound exams (primary end-point) was 0% in the enoxaparin-treated group but 27.7% in the control group ( $P = 0.001$ ). Perhaps more impressive were the secondary end-points of hepatic decompensation and overall and transplant-free survival, all of which occurred with an incidence implying benefit with enoxaparin. Although platelet count decreased in the enoxaparin group by nearly 50%, there was no relationship of treatment arm to the rare occurrence of bleeding complications. Perhaps the most intriguing finding of this study was the fact that the benefits of enoxaparin on rates of hepatic decompensation and survival occurred independently of PVT prevention, supporting the hypothesis that thrombosis of the hepatic microcirculation contributes to the progression of liver disease [25]. Although anticoagulation to prevent PVT and complications of cirrhosis requires confirmation before its routine application in clinical practice, this pilot study illustrates many of the emerging concepts regarding global hemostasis in patients with cirrhosis and how they might be managed in the future.

The treatment of existing PVT in patients with cirrhosis has been recently summarized by Valla and Rautou [41]. In four retrospective studies using enoxaparin, two of which included conversion to oral vitamin K antagonists (i.e., warfarin), complete recanalization occurred in 42–75%, and no recanalization occurred in 17–53% of patients. Importantly, there were no bleeding-related deaths due to anticoagulation in any of these studies. In another large, multicenter natural history study of patients with splanchnic vein thrombosis, 28% of whom had cirrhosis (Fig. 13.8), the incidence of

**Fig. 13.8** Effects of anticoagulation on bleeding and thrombotic complications in 604 patients with splanchnic venous thrombosis. A variety of underlying risk factors are included, with 167 (28%) having cirrhosis as the underlying risk factor (most common). Patients in the “AC” group received continuous anticoagulation and those in the “AC stopped” group received intermittent anticoagulation. (Adapted from Ageno, et al. *JAMA Internal Med.* 2015; 175: 1474) [37]





major bleeding was actually lower in patients who received at least some anticoagulation compared to those who did not, while the incidence of thrombotic complications was lower as long as anticoagulants were continued [37]. The presence of PVT for fewer than 6 months may be an indication for anticoagulation, since recanalization rarely occurs later [42]. Conversely, recanalization on anticoagulation usually occurs within 6 months. Insertion of transjugular intrahepatic porto-systemic shunt through a portal thrombus has also been tested to re-establish portal flow and lower portal pressure in cases where anticoagulation has not resulted in recanalization [42, 43], but has not been studied in a randomized fashion [44].

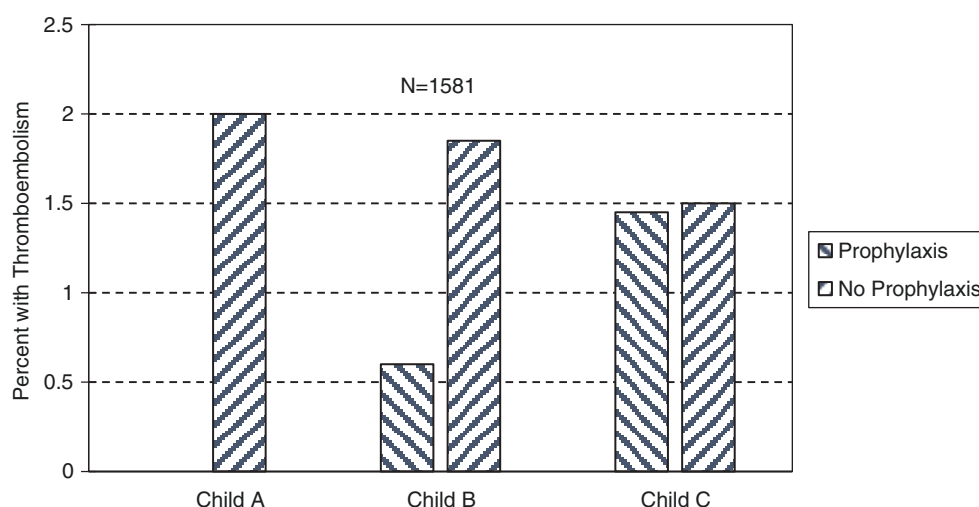
A large retrospective study of patients with cirrhosis (N = 1581) has shown that anticoagulant prophylaxis against VTE can be administered safely, but its efficacy may be limited to patients with mild-to-moderate liver failure [45]. As shown in Fig. 13.9, the administration of standard or low molecular weight heparin (LMWH) decreased the incidence of VTE in patients with Child A/B, but not Child C, class cirrhosis. Bleeding complications were observed in 0.3% of subjects who received heparin/LMWH, but in 1.1% of those who did not (P = 0.13). The absence of benefit in Child C class patients is likely due to lower levels of AT.

The dosing and choice of anticoagulants in patients with cirrhosis and thrombotic complications has not been studied extensively, but raises unique challenges. Levels of vitamin K-dependent coagulation factors are decreased; consequently, in cirrhotic patients with elevated INR at baseline, it is not clear how to dose warfarin. Thrombin generation in patients with cirrhosis appears to be more responsive to

enoxaparin in proportion to the severity of liver failure compared to controls, despite lower AT levels in plasma [46]. Renal failure complicating cirrhosis may also increase the potency of enoxaparin. Thus, it is not clear how to dose heparin/LMWH safely in patients with cirrhosis. Direct factor Xa inhibitors (apixaban and rivaroxaban) may have a safety profile similar to warfarin in a small pilot study of cirrhotics [47], but also may be less potent in patients with cirrhosis compared to healthy controls [48]. Obviously, additional studies are urgently needed to define how to use anticoagulants in patients with cirrhosis, who may be at additional risk to bleeding complications from their use.

### 13.2.5 Destabilizing Re-balanced Hemostasis in Patients with Cirrhosis

The discussion above suggests that global hemostasis in patients with stable cirrhosis exists in a re-balanced equilibrium tipped toward a slightly pro-coagulant state. However, patients with cirrhosis often become unstable and develop acute-on-chronic liver failure (ACLF), the syndrome of acutely decompensated cirrhosis leading to organ failure [49]. Hemostasis has not been studied in patients with ACLF since formal definition was proposed by Moreau et al. [50], but coagulopathy is part of the definition of ACLF by virtue of its inclusion in the Sequential Organ Failure Assessment Score, from which criteria for ACLF are partly derived. Future studies are, therefore, likely to identify ACLF as a cause of unbalanced hemostasis in patients with cirrhosis, tipped toward bleeding or thrombosis. For example, infection



**Fig. 13.9** Rate of venous thromboembolism stratified by severity of liver failure (Child-Pugh Class) and receipt of anticoagulant prophylaxis. “Prophylaxis” refers to the administration of heparin or low molecular weight heparin to prevent VTE in 1581 patients with cirrhosis. Bleeding complications were observed in 0.3% of patients who

received anticoagulant prophylaxis and 1.1% of those who did not (P = 0.13). There were no cases of VTE in patients with Child A class cirrhosis who received anticoagulant prophylaxis. (Adapted from Barclay, et al. *Pharmacotherapy*. 2013; 33: 375) [45]

is the most common trigger of ACLF [51, 52] and has deleterious effects on global hemostasis as assessed by TEG [53], at least partly due to the elaboration of endogenous heparinoids from endothelial cells [54]. Other destabilizing factors include acute gastrointestinal bleeding *per se*, which decreases maximum clot strength in TEG [55]. Finally, endothelial dysfunction and renal failure, which complicate cirrhosis frequently, impair platelet-endothelial interaction, leading to a tipped balance toward bleeding. Destabilized hemostasis in patients with cirrhosis may also result in thrombosis [56]. Precipitating factors which tip the balance toward thrombosis include increased platelet number (for example, after overtransfusion of platelets or use of thrombopoietin agonists such as eltrombopag) or platelet activation and generation of pro-coagulant microparticles (MPs) by infection, endotoxemia or the development of hepatocellular carcinoma (HCC) [57]. These confounders have led to the conclusion that the state of hemostasis in stable cirrhotics is “fragile and not as stable,” despite re-balance in the unperturbed state.

### 13.3 Acute Liver Failure

#### 13.3.1 Clinical Features of Hemostasis and Bleeding Risk in Patients with ALF

Patients with ALF are perceived to have a bleeding tendency primarily on the basis of profoundly elevated INR, which can be unmeasurably high. The INR is an important prognostic indicator in ALF [58], but not because it predicts bleeding complications. In fact, the INR of patients with and without bleeding complications is not significantly different over the first week after admission for ALF (Stravitz and the ALF Study Group, unpublished data).

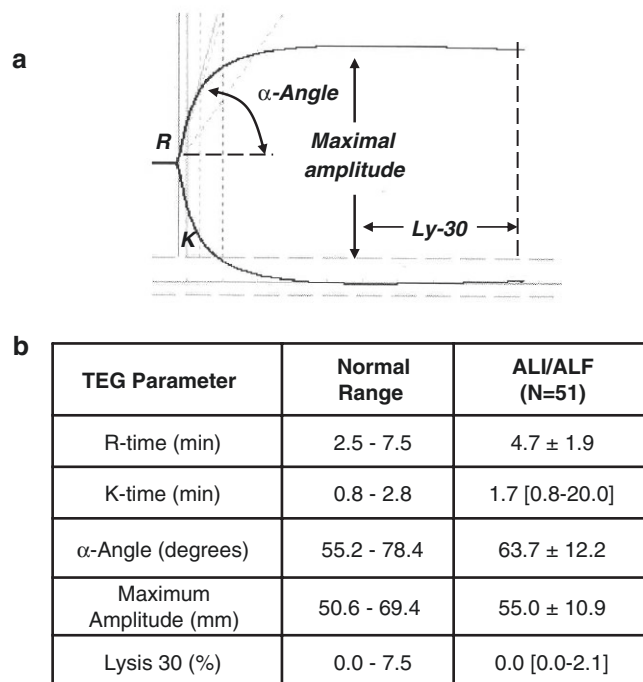
Patients with ALF also develop thrombocytopenia, although on average, to a less impressive nadir than patients with cirrhosis [3]. The mechanisms by which platelet counts decrease in ALF differ significantly from those in cirrhosis, since portal hypertension and hypersplenism are milder in the former [59]. Although thrombopoietin levels are low due to massive hepatic necrosis, they do not correlate with the platelet count [60], and therefore are not considered a major reason for thrombocytopenia in ALF. In contrast, platelet activation by the SIRS, often dramatic in ALF [4], probably leads to platelet clearance [3]. Production of platelet-derived MPs during this activation process provides experimental evidence supporting this hypothesis [61].

In an apparent clinical paradox, however, patients with ALF seldom bleed. In an analysis of nearly 1800 patients enrolled in the ALF Study Group Registry between 1998–2014, spontaneous and post-procedural bleeding complications were observed in a small minority (~10%) of patients, and were usually not clinically significant. Most bleeding complications were due to upper gastrointestinal bleeding, probably from gastric mucosal

injury, and did not require specific intervention or blood transfusion. Post-procedural bleeding was also uncommon, but serious and often fatal when due to insertion of an intracranial pressure (ICP) monitor (Stravitz and the ALF Study Group, unpublished data). These recent data are in sharp contrast to older series, in which bleeding complications occurred in 50–70%, and were the proximal cause of death in  $\geq 30\%$ , of patients with ALF [62–64]. Improvement in intensive care management has led to a marked decline in bleeding complications in critically ill patients in general, however [65].

#### 13.3.2 ALF as a State of Re-balanced Hemostasis

The conundrum of a perceived bleeding tendency in the face of infrequent bleeding complications in patients with ALF has been recently explored. As shown in Fig. 13.10, global

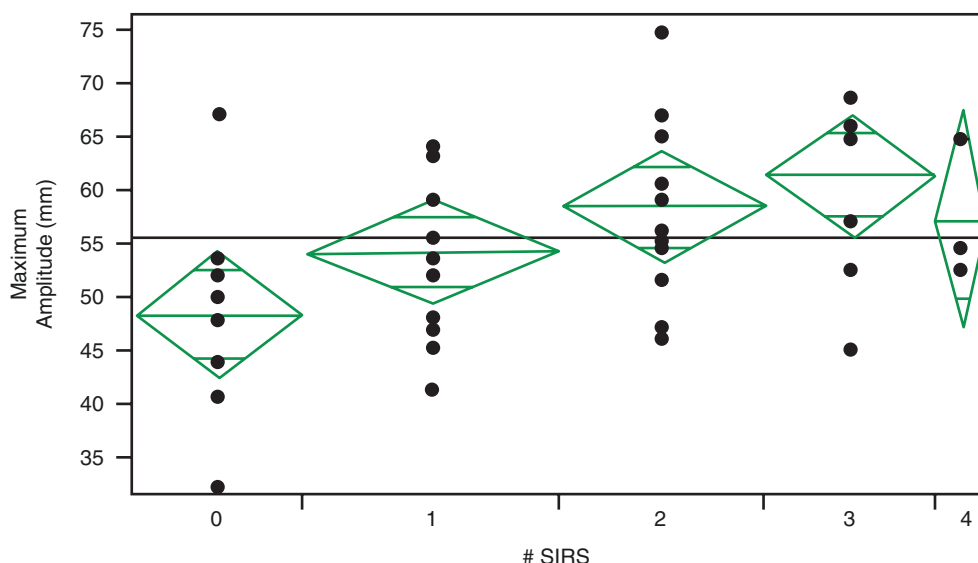


**Fig. 13.10** Use of thromboelastography (TEG) to define the state of hemostasis in whole blood from patients with acute liver injury/failure. (a) Representative TEG tracing from a patient with ALF due to an acetaminophen overdose. The tracing shows a hypercoagulable profile despite an INR of 4.2 and factor VII level of 4% of normal. (b) Mean/median TEG parameters in 51 patients with ALI/ALF, and normal values of these parameters. (Adapted from: Stravitz, et al., *J Hepatol.* 2012; 56: 129) [67]. R-time (in minutes): the latency of clot formation. K-time (in minutes): the time from initial fibrin formation required to reach a clot firmness of 20 mm. α-Angle (in degrees): the kinetics of clot formation, measuring the rate of fibrin formation and cross-linking on platelets. Maximum amplitude (in mm): measures the maximal clot strength. Lysis at 30 min (Lysis-30; in percent): clot dissolution 30 min after reaching maximum amplitude, a measure of fibrinolysis

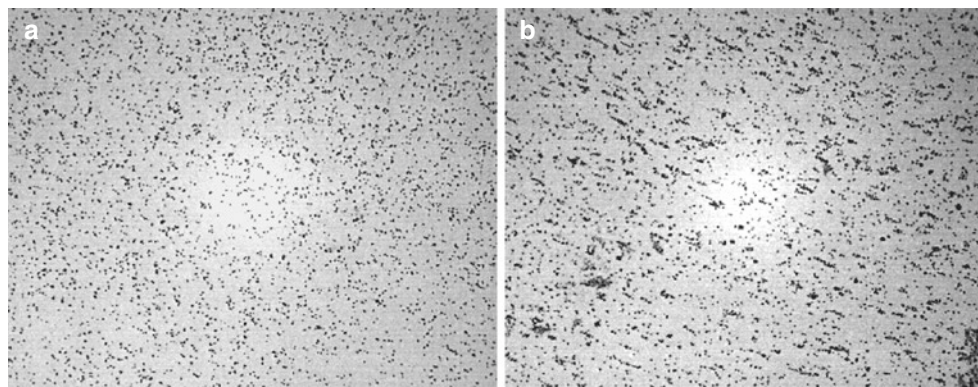
hemostasis as assessed by TEG is usually normal. The representative TEG shown was assayed in whole blood from a patient with a serious acetaminophen overdose, in whom the INR at the same time was 4.2, and the factor VII level was 4% of normal, and shows a *hypercoagulable* profile [20]. Two obvious contributors to hypercoagulability in this patient were a simultaneous factor VIII level of 558% of normal, high vWF levels, and only mild thrombocytopenia ( $163 \times 10^9/L$ ). Very high factor VIII and vWF levels are a consistent finding in ALF (Fig. 13.4) [66, 67], and are probably caused by activation and injury of vascular endothelium [68]. In a series of 51 patients with acute liver injury (a milder form of ALF without encephalopathy) and ALF, the mean/median TEG parameters were well within normal limits (Fig. 13.10, table). Other laboratories have confirmed these findings using TEG [69], and other studies have shown thrombin generation in the presence of TM in plasma from ALF patients is similar to normal healthy controls, results similar to those in patients with cirrhosis (Fig. 13.3) [70, 71].

In the setting of often profoundly decreased pro-hemostatic factors, these data suggest that hemostasis remains re-balanced in patients with ALF, and therefore, compensatory mechanisms must exist. As for cirrhotics, pro- and anti-coagulant, liver-derived coagulation factors decrease proportionally in the face of liver failure [67]. In contrast to the case with cirrhosis, however, profound activation of the SIRS by the cytokine storm which ensues after the primary liver injury appears to be a major driver of compensation. The result can be semi-quantitated in TEG assays, which show maximum amplitude of clot formation increases commensurate with the number of SIRS components on admission to the hospital (Fig. 13.11). The responsible mechanisms of this increase probably include increased factor VIII and vWF levels [66, 67]. The effects of high vWF can be observed in perfused chambers mimicking plasma flow. As shown in Fig. 13.12, the same number of platelets from normal patients were incubated either with plasma from normal healthy donors (Panel A), or patients with ALF

**Fig. 13.11** The relationship of maximum blood clot strength (amplitude) in thromboelastography according to the number of positive elements of the systemic inflammatory response syndrome (SIRS) on admission to the hospital for acute liver failure. (Adapted from: Stravitz, et al., *J Hepatol.* 2012; 56: 129) [67]



**Fig. 13.12** Platelet aggregation in plasma from normal healthy controls and patients with acute liver failure. The same number of platelets were added to perfusion chambers containing plasma from normal healthy control subjects (a), or from patients with ALF (b). The increased platelet aggregation in platelets incubated in plasma from ALF patients compared to control is due to increased vonWillebrand factor in the latter. (Adapted from Hugenholtz, et al. *Hepatology.* 2013; 58: 752) [66]

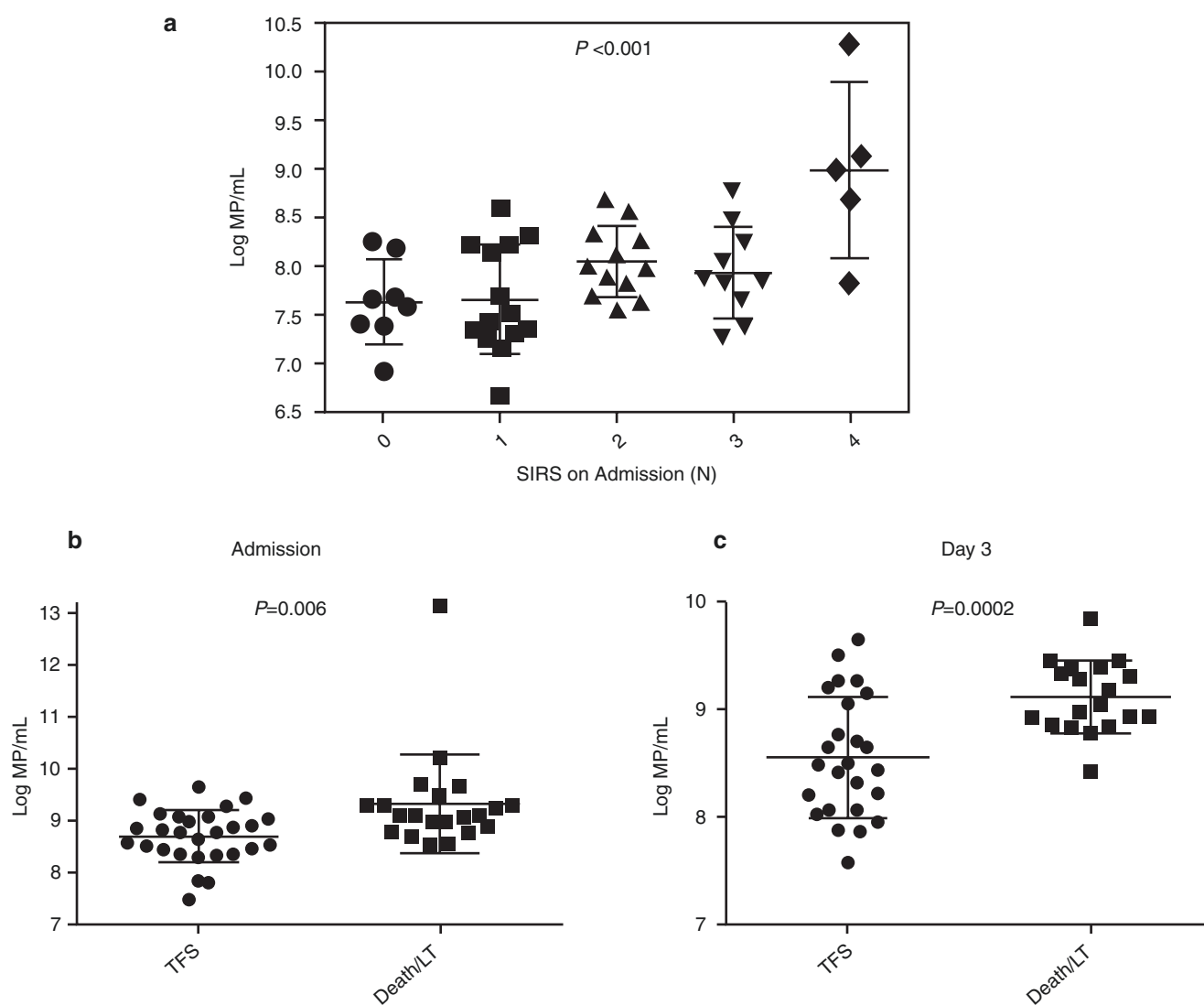


(Panel B). Platelet aggregation is much more dramatic in the latter, a demonstration of the effects of increased vWF release from endothelial cells.

The SIRS also appears to contribute to re-balanced hemostasis in patients with ALF by activating platelets, yielding highly pro-coagulant MPs [61]. MPs are everted fragments (<1  $\mu$ m) of plasma membrane derived from many cell types in response to the SIRS [72]. The eversion process exposes phosphatidylserine (PS), usually segregated to the inner leaflet of the plasma membrane. With exposure to the exterior of the MP, PS activates the coagulation cascade synergistically with tissue factor (TF) [73], the primary activator of the extrinsic coagulation cascade. The source of TF within the necrotic liver appears to be hepatocytes, which normally

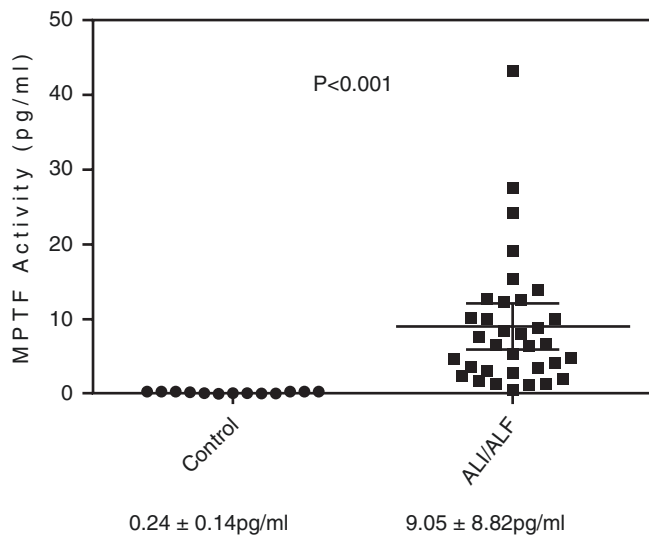
express low levels, but are thought to de-encrypt TF in response to toxic injury, including acetaminophen overdose [74]. In patients with ALF, MPs are primarily platelet-derived, increase in proportion to the number of SIRS components (Fig. 13.13a), and are highly pro-coagulant as they also contain TF (Fig. 13.14). In fact, MP-associated TF activity, a measure of pro-coagulant activity, is higher than in other disease states characterized by hypercoagulability (HIV, malignancy, sickle cell disease) [61]. MPs may also mediate the multiorgan system failure (MOSF) of ALF, the primary cause of death, and are associated with death or the need for liver transplantation (Fig. 13.13b, c).

Defective fibrinolysis may also serve to re-balance low pro-coagulant factors and fibrinogen in patients with

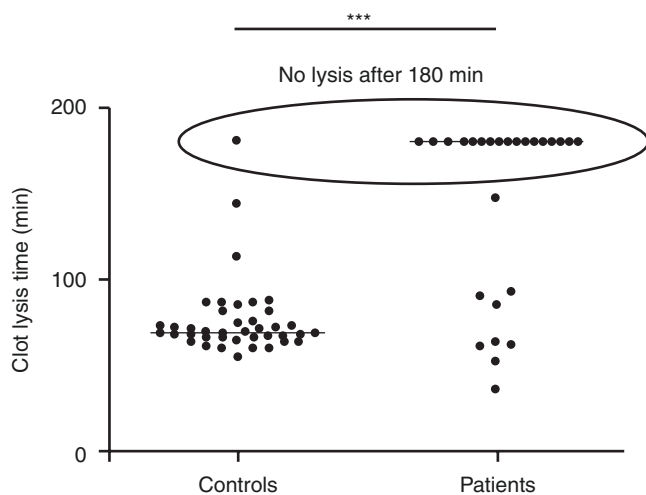


**Fig. 13.13** Concentration of microparticles in plasma of patients with acute liver failure. (a). Log<sub>10</sub> microparticles (MP)/ml vs. number of positive SIRS criteria on admission to the hospital. (b) Log<sub>10</sub> MP/ml on admission to the hospital in patients with ALF according to outcome

(TFS, transplant-free survival; death/LT, death or liver transplantation). (c) Log<sub>10</sub> MP/ml on day 3 of hospitalization in patients with ALF according to outcome. (Adapted from: Stravitz, et al. *Hepatology*. 2013; 58: 304) [61]



**Fig. 13.14** Microparticle tissue factor (MPTF) activity in plasma from patients with acute liver injury/failure and normal healthy controls. MPTF activity is a measure of pro-coagulant activity, as it reflects the synergistic effect of phosphatidylserine (on the everted surface of MPs) and tissue factor on the production of factor Xa. Means  $\pm$  SD are shown. (Adapted from: Stravitz, et al. *Hepatology*. 2013; 58: 304) [61]



**Fig. 13.15** Whole blood clot lysis time in plasma from patients with acute liver injury/failure and normal healthy controls. (Adapted from: Lisman, et al. *J Thromb Haemost* 2012; 10: 1312) [70]

ALF. Although older studies suggested that patients with ALF often develop a condition resembling disseminated intravascular coagulation (DIC) [75], ALF patients do not have the classical features of consumptive coagulopathy because factor VIII levels are markedly elevated, not low. Analysis of clot lysis *in vitro* has shown that fibrinolysis is markedly slower in patients with ALF compared to healthy controls, with clot lysis in many of the former unmeasurably high (Fig. 13.15).

### 13.3.3 ALF as a Hypercoagulable State

Similar to patients with cirrhosis, the above data suggest that hemostasis in patients with ALF exists in a re-balanced state slightly biased toward thrombosis. Few clinical studies of thrombotic complications in ALF exist, but several observations strongly suggest the presence of relative hypercoagulability. Hemostasis in whole blood by TEG has implied a hypercoagulable state in 25–35% of patients with ALF [67, 69]. RRT circuits frequently thrombose in patients with ALF [29], possibly the result of increased soluble TF and MP production [76]. Early studies documented fibrin deposition in the liver of patients with acetaminophen overdose [75], and subsequent data in animal models of ALF have correlated the degree of coagulation activation and extent of necrosis, implying that intrahepatic thrombosis may cause a secondary ischemic hit after the primary liver injury. Furthermore, heparin ameliorates acetaminophen-induced hepatotoxicity [77]. Finally, ALF patients with MOSF develop peripheral tissue hypoxia leading to lactic acidosis, caused in part by microthrombi in peripheral microcirculation [78]. Thus, although gross thrombotic complications in ALF may not be a prominent feature of the syndrome, thrombosis of the hepatic and systemic microvasculature is likely to be a major contributor to the pathogenesis of the syndrome and to poor outcome.

### 13.3.4 Management of Hemostatic Abnormalities in Patients with ALF

There are few data to guide clinicians in using blood and blood products or anticoagulants in patients with ALF, and recommendations are primarily based upon personal experience. As a preamble, several points will be re-emphasized. First, spontaneous and post-procedural bleeding complications are uncommon in patients with ALF, and when they occur, they reflect the severity of the secondary SIRS and systemic complications rather than the severity of the primary liver injury. Consequently, they can be anticipated by a low platelet count, but not a high INR. The severity of bleeding complications in patients with ALF is usually mild and self-limited, not requiring of RBC transfusion. However, bleeding complications portend poor outcome, most likely due to their association with MOSF, but not bleeding *per se*. The bleeding complication with highest morbidity and mortality in patients with ALF is intracranial bleeding after ICP monitor placement; although uncommon (~5%) [79], it has a high mortality (~50%). These observations are based upon extensive review of the ALF Study Group Registry of nearly 2000 patients, but have not yet been published (Stravitz and the ALF Study Group, unpublished data).



The decision to transfuse patients with ALF should not be taken lightly in the absence of a significant bleeding complication or before highest-risk procedure, such as ICP monitor placement. Primarily, transfusion of plasma removes the most important prognostic indicator of spontaneous recovery of the liver, as the clinician can no longer rely on the trend in INR. It has also been observed in the ALF Study Group Registry that transfusion of RBC, platelets, or plasma is associated with a nearly 50% increase in death or liver transplantation at day 21 after admission. Most probably, the need for transfusion of any blood component selects for the more acutely ill patients, but also raises the possibility that transfusions cause harm. As discussed above, patients with ALF may be hypercoagulable and systemic and intrahepatic activation of coagulation increases; it is therefore plausible that blood and product transfusions cause harm by exacerbating microvascular thrombosis, exacerbating not only the liver injury, but also MOSF.

When, therefore, should clinicians consider transfusion in patients with ALF? As a treatment for active bleeding, they should be reserved for clinically significant bleeding. As prophylaxis, they should be reserved for high-risk procedures, such as percutaneous liver biopsy or placement of an ICP monitor. A goal INR should probably not be used. Rather, ~2 units of plasma transfused within roughly an hour before the procedure without repeating the INR might be considered since this strategy repletes pro-coagulant factors to achieve a minimal level to support thrombin generation. Platelet transfusions should be considered when  $< 60 \times 10^9/L$ , based upon the work in cirrhotics by Tripodi et al. [14], which has not yet been reproduced in patients with ALF. Fibrinogen repletion as cryoprecipitate should be considered when plasma concentrations are  $< 100$  mg/dl. The use of TEG to guide repletion, similar to methods adopted by liver transplant anesthesiologists [80], would be reasonable, if available. Treatment of the underlying precipitating factor of the bleeding should always accompany transfusions. The precipitating factors resemble those described for cirrhosis, most importantly, infection and renal failure.

The use of anticoagulants in patients with ALF is equally based upon local experience and practice. During RRT, it has been recommended that citrate be avoided because of the decreased hepatic capacity to metabolize citrate. However, a recent report from the King's College has suggested that citrate is, in fact, probably safe [81]. The use of heparin in RRT is also probably safe in patients with ALF, although may not be as effective as in other critically ill patients without liver failure because of low AT levels in the former. Some form of VTE prophylaxis should be strongly considered. Pneumatic compression devices may be more appealing to clinicians in the setting of renal failure or severe thrombocytopenia, but low-dose heparins have been used without complications (RTS, personal observations).

Several studies have advocated the use of rVIIa before high risk procedures such as ICP monitor placement [82]. Although the strategy temporarily normalizes the INR without the risk of volume overload of plasma infusion, it obfuscates the use of the INR for prognosis, any may exacerbate the hypercoagulable state of ALF; indeed, serious thrombotic complications of rFVIIa have been reported in patients with ALF [83].

## Conclusions

In conclusion, stable patients with liver disease may be considered to have re-balanced hemostasis apart from the bleeding risk from complications of portal hypertension, the risk of which is determined by the severity of portal hypertension, not deficiencies in hemostasis. However, hemostasis in patients with severe acute or chronic liver disease is in a fragile state of compensation, the balance of which may be tipped toward bleeding or thrombosis by a number of precipitating factors. Unfortunately, few clinical studies have proved the safety of withholding pro-coagulant therapies, particularly before high-risk invasive procedures. Further studies are urgently needed to determine whether blood product transfusions cause harm in patients with severe acute or chronic liver disease, since a tipped balance toward hypercoagulability appears to contribute to the pathogenesis of liver injury and complications in both syndromes.

## References

1. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011 Jul 14;365(2):147–56.
2. de Franchis R, Primignani M. Why do varices bleed? *Gastroenterol Clin N Am*. 1992 Mar;21(1):85–101.
3. Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lisman T, Lee WM. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. *Clin Gastroenterol Hepatol*. 2016 Apr;14(4):613–20.
4. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology*. 2000 Oct;32(4 Pt 1):734–9.
5. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol*. 2010 Aug;53(2):362–71.
6. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion*. 2005 Sep;45(9):1413–25.
7. Patel JJ, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, Walker TG, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol*. 2012 Jun;23(6):727–36.
8. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. *Hepatology*. 2009 Mar;49(3):1017–44.
9. Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation fac-

- tors in plasma from patients with cirrhosis. *Gastroenterology*. 2009 Dec;137(6):2105–11.
10. Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. *Semin Thromb Hemost*. 2015 Jul;41(5):468–73.
  11. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez AJ, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology*. 2004 Oct;127(4):1123–30.
  12. Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. *Hepatology*. 2008 May;47(5):1604–14.
  13. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology*. 2005 Mar;41(3):553–8.
  14. Tripodi A, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, et al. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology*. 2006 Aug;44(2):440–5.
  15. Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology*. 2006 Jul;44(1):53–61.
  16. Lancellotti S, Basso M, Veca V, Sacco M, Riccardi L, Pompili M, et al. Presence of portal vein thrombosis in liver cirrhosis is strongly associated with low levels of ADAMTS-13: a pilot study. *Intern Emerg Med*. 2016 May;24
  17. Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy – a prospective audit. *Intensive Care Med*. 1999 May;25(5):481–5.
  18. Massicotte L, Thibeault L, Roy A. Classical notions of coagulation revisited in relation with blood losses, transfusion rate for 700 consecutive liver transplantations. *Semin Thromb Hemost*. 2015 Jul;41(5):538–46.
  19. De PL, Bianchini M, Montalti R, De MN, Di MT, Begliomini B, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. *Hepatology*. 2016 Feb;63(2):566–73.
  20. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (NY)*. 2012 Aug;8(8):513–20.
  21. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007 Sep;46(3):922–38.
  22. Castaneda B, Morales J, Lionetti R, Moitinho E, Andreu V, Perez-Del-Pulgar S, et al. Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats. *Hepatology*. 2001 Apr;33(4):821–5.
  23. Giannini EG, Stravitz RT, Caldwell SH. Correction of hemostatic abnormalities and portal pressure variations in patients with cirrhosis. *Hepatology*. 2014 Oct;60(4):1442.
  24. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013 Jan 3;368(1):11–21.
  25. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology*. 1995 May;21(5):1238–47.
  26. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol*. 2006 Jul;101(7):1524–8.
  27. Gulley D, Teal E, Suvannasankha A, Chalasani N, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhosis patients. *Dig Dis Sci*. 2008 Nov;53(11):3012–7.
  28. Sogaard KK, Horvath-Puho E, Gronbaek H, Jepsen P, Vilstrup H, Sorensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol*. 2009 Jan;104(1):96–101.
  29. Agarwal B, Shaw S, Shankar HM, Burroughs AK, Davenport A. Continuous renal replacement therapy (CRRT) in patients with liver disease: is circuit life different? *J Hepatol*. 2009 Sep;51(3):504–9.
  30. Ben-Ari Z, Panagou M, Patch D, Bates S, Osman E, Pasi J, et al. Hypercoagulability in patients with primary biliary cirrhosis and primary sclerosing cholangitis evaluated by thrombelastography. *J Hepatol*. 1997 Mar;26(3):554–9.
  31. Northup PG, Argo CK, Shah N, Caldwell SH. Hypercoagulation and thrombophilia in nonalcoholic fatty liver disease: mechanisms, human evidence, therapeutic implications, and preventive implications. *Semin Liver Dis*. 2012 Feb;32(1):39–48.
  32. Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. *Liver Transpl*. 2015 Aug;21(8):1016–21.
  33. Potze W, Siddiqui MS, Boyett SL, Adelmeijer J, Daita K, Sanyal AJ, et al. Preserved hemostatic status in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2016 Jun 11;65:980–7.
  34. Tripodi A, Fracanzani AL, Primignani M, Chantarangkul V, Clerici M, Mannucci PM, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2014 Jul;61(1):148–54.
  35. Verrijken A, Francque S, Mertens I, Prawitt J, Caron S, Hubens G, et al. Prothrombotic factors in histologically proven nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2014 Jan;59(1):121–9.
  36. Tsochatzis EA, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. *Aliment Pharmacol Ther*. 2010 Feb 1;31(3):366–74.
  37. Ageno W, Riva N, Schulman S, Beyer-Westendorf J, Bang SM, Senzolo M, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. *JAMA Intern Med*. 2015 Sep;175(9):1474–80.
  38. Nery F, Chevrete S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology*. 2015 Feb;61(2):660–7.
  39. Garcia-Pagan JC, Valla DC. Portal vein thrombosis: a predictable milestone in cirrhosis? *J Hepatol*. 2009 Oct;51(4):632–4.
  40. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology*. 2012 Nov;143(5):1253–60.
  41. Valla DC, Rautou PE. The coagulation system in patients with end-stage liver disease. *Liver Int*. 2015 Jan;35(Suppl 1):139–44.
  42. Senzolo M, Sartori M, Rossetto V, Burra P, Cillo U, Boccagni P, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int*. 2012 Jul;32(6):919–27.
  43. Luca A, Miraglia R, Caruso S, Milazzo M, Sapere C, Maruzzelli L, et al. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. *Gut*. 2011 Jun;60(6):846–52.
  44. Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2014 Jul;11(7):435–46.
  45. Barclay SM, Jeffres MN, Nguyen K, Nguyen T. Evaluation of pharmacologic prophylaxis for venous thromboembolism in patients with chronic liver disease. *Pharmacotherapy*. 2013 Apr;33(4):375–82.
  46. Senzolo M, Rodriguez-Castro KI, Rossetto V, Radu C, Gavasso S, Carraro P, et al. Increased anticoagulant response to low-molecular-

- weight heparin in plasma from patients with advanced cirrhosis. *J Thromb Haemost*. 2012 Sep;10(9):1823–9.
47. Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, Caldwell SH. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. *Dig Dis Sci*. 2016 Jun;61(6):1721–7.
  48. Potte W, Adelmeijer J, Lisman T. Decreased in vitro anticoagulant potency of Rivaroxaban and Apixaban in plasma from patients with cirrhosis. *Hepatology*. 2015 Apr;61(4):1435–6.
  49. Stravitz RT. Acute-on-chronic liver failure – no longer an entity without definition. *Nat Rev Gastroenterol Hepatol*. 2014 Oct;11(10):580–1.
  50. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013 Jun;144(7):1426–37.
  51. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology*. 2014 Jul;60(1):250–6.
  52. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol*. 2014 Nov;61(5):1038–47.
  53. Papatheodoridis GV, Patch D, Webster GJ, Brooker J, Barnes E, Burroughs AK. Infection and hemostasis in decompensated cirrhosis: a prospective study using thrombelastography. *Hepatology*. 1999 Apr;29(4):1085–90.
  54. Montalto P, Vlachogiannakos J, Cox DJ, Pastacaldi S, Patch D, Burroughs AK. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *J Hepatol*. 2002 Oct;37(4):463–70.
  55. Chau TN, Chan YW, Patch D, Tokunaga S, Greenslade L, Burroughs AK. Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding. *Gut*. 1998 Aug;43(2):267–71.
  56. Tapper EB, Robson SC, Malik R. Coagulopathy in cirrhosis – the role of the platelet in hemostasis. *J Hepatol*. 2013 Oct;59(4):889–90.
  57. Rautou PE, Bresson J, Sainte-Marie Y, Vion AC, Paradis V, Renard JM, et al. Abnormal plasma microparticles impair vasoconstrictor responses in patients with cirrhosis. *Gastroenterology*. 2012 Jul;143(1):166–76.
  58. Harrison PM, O'Grady JG, Keays RT, Alexander GJ, Williams R. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ*. 1990 Oct 27;301(6758):964–6.
  59. Valla D, Flejou JF, Lebre D, Bernuau J, Rueff B, Salzmann JL, et al. Portal hypertension and ascites in acute hepatitis: clinical, hemodynamic and histological correlations. *Hepatology*. 1989 Oct;10(4):482–7.
  60. Schiodt FV, Balko J, Schilsky M, Harrison ME, Thornton A, Lee WM. Thrombopoietin in acute liver failure. *Hepatology*. 2003 Mar;37(3):558–61.
  61. Stravitz RT, Bowling R, Bradford RL, Key NS, Glover S, Thacker LR, et al. Role of procoagulant microparticles in mediating complications and outcome of acute liver injury/acute liver failure. *Hepatology*. 2013 Jul;58(1):304–13.
  62. Gazzard BG, Portmann B, Murray-Lyon IM, Williams R. Causes of death in fulminant hepatic failure and relationship to quantitative histological assessment of parenchymal damage. *Q J Med*. 1975 Oct;44(176):615–26.
  63. Tandon BN, Joshi YK, Tandon M. Acute liver failure. Experience with 145 patients. *J Clin Gastroenterol*. 1986 Dec;8(6):664–8.
  64. Ritt DJ, Whelan G, Werner DJ, Eigenbrodt EH, Schenker S, Combes B. Acute hepatic necrosis with stupor or coma. An analysis of thirty-one patients. *Medicine (Baltimore)*. 1969 Mar;48(2):151–72.
  65. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015 May;41(5):833–45.
  66. Hugenholtz GC, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT, Lisman T. An unbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. *Hepatology*. 2013 Aug;58(2):752–61.
  67. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. *J Hepatol*. 2012 Jan;56(1):129–36.
  68. Williams AM, Langley PG, Osei-Hwediah J, Wendon JA, Hughes RD. Hyaluronic acid and endothelial damage due to paracetamol-induced hepatotoxicity. *Liver Int*. 2003 Apr;23(2):110–5.
  69. Agarwal B, Wright G, Gatt A, Riddell A, Vemala V, Mallett S, et al. Evaluation of coagulation abnormalities in acute liver failure. *J Hepatol*. 2012 Oct;57(4):780–6.
  70. Lisman T, Bakhtiari K, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. *J Thromb Haemost*. 2012 Jul;10(7):1312–9.
  71. Habib M, Roberts LN, Patel RK, Wendon J, Bernal W, Arya R. Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. *Liver Int*. 2014 May;34(5):672–8.
  72. Owens AP III, Mackman N. Microparticles in hemostasis and thrombosis. *Circ Res*. 2011 May 13;108(10):1284–97.
  73. Key NS. Analysis of tissue factor positive microparticles. *Thromb Res*. 2010 Apr;125(Suppl 1):S42–5.
  74. Sullivan BP, Kopec AK, Joshi N, Cline H, Brown JA, Bishop SC, et al. Hepatocyte tissue factor activates the coagulation cascade in mice. *Blood*. 2013 Mar 7;121(10):1868–74.
  75. Hillenbrand P, Parbhoo SP, Jedrychowski A, Sherlock S. Significance of intravascular coagulation and fibrinolysis in acute hepatic failure. *Gut*. 1974 Feb;15(2):83–8.
  76. Agarwal B, Gatt A, Riddell A, Wright G, Chowdhury P, Jalan R, et al. Hemostasis in patients with acute kidney injury secondary to acute liver failure. *Kidney Int*. 2013 Jul;84(1):158–63.
  77. Ganey PE, Luyendyk JP, Newport SW, Eagle TM, Maddox JF, Mackman N, et al. Role of the coagulation system in acetaminophen-induced hepatotoxicity in mice. *Hepatology*. 2007 Oct;46(4):1177–86.
  78. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med*. 1991 Jun 27;324(26):1852–7.
  79. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl*. 2005 Dec;11(12):1581–9.
  80. Mallett SV. Clinical Utility of Viscoelastic Tests of Coagulation (TEG/ROTEM) in patients with liver disease and during liver transplantation. *Semin Thromb Hemost*. 2015 Jul;41(5):527–37.
  81. Patel S, Wendon J. Regional citrate anticoagulation in patients with liver failure – time for a rethink? *Crit Care*. 2012;16(5):153.
  82. Shami VM, Caldwell SH, Hespeneide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl*. 2003 Feb;9(2):138–43.
  83. Pavesi P, Bonadonna A, Beaubien J, Labrecque P, Pernod G, Letoublon C, et al. FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: a report of four cases. *Can J Anaesth*. 2005 Jan;52(1):26–9.

Panna A. Codner, Beth Taylor, and Jayshil J. Patel

## Abstract

Nutritional support in the patient with liver disease is a complex challenge. The liver is a key organ in many metabolic processes with considerable reserve. Multiple etiologies and duration of liver disease factor into the challenge of managing nutritional support in these patients. Despite these obstacles, the basic tenants of nutrition therapy including risk assessment, attention to protein and energy requirements, provision of nutrients in compensated and decompensated states, and monitoring and treatment of complications enable these patients to receive the optimal benefits of nutritional therapy. The use of body composition assessment with advanced imaging has expanded our nutritional assessment toolbox and is predictive of quality of life, survival, and outcomes after surgery in cirrhosis and possibly after organ transplantation.

## Keywords

Liver disease • Liver failure • Nutrition • Enteral nutrition • Parenteral nutrition • Branched chain amino acids • Sarcopenia • Liver transplant • Organ transplant

## 14.1 Background

### 14.1.1 Introduction

Nutritional support for liver disease patients is challenging. The pivotal role of the liver in metabolism and the loss of normal metabolic reserves during liver failure contributes to the complexity of nutritional therapy, as do the wide variations in the cause and severity of liver disease. Assessing nutritional risk in this population can be challenging and

may yield unreliable results, contributing to a lack of specific recommendations in this population.

The unique histology and anatomy of the liver facilitate its participation in a wide array of critical functions. Many cell types exist in the liver, including hepatocytes, Kupffer cells, stellate cells, bile duct epithelium, and sinusoidal endothelial cells. Liver cells are responsible for processes such as amino acid metabolism, ammonia production, glycogen storage, and cytokine and hormone production. Hepatic Kupffer cells are the largest reservoir of fixed macrophages in the body and play a critical role in the entry of gut-derived toxins into the portal circulation, which is supplied by both the portal vein and the hepatic arteries. The hepatic portal vein supplies 75% of the blood to the liver while the hepatic arteries supply the remaining 25%. The hepatic oxygen demand is equally satisfied by the portal vein and hepatic arteries. The liver receives nutrient-rich blood directly from the gastrointestinal tract, facilitating its essential role in carbohydrate, protein, and fatty acid metabolism and the bile production necessary for intestinal fat absorption.

P.A. Codner, M.D., F.A.C.S. (✉)

Division of Trauma and Critical Care Medicine, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI 53226, USA  
e-mail: [pcodner@mcw.edu](mailto:pcodner@mcw.edu)

B. Taylor, DCN, RDN-AP, CNSC, FCCM

Surgical/Trauma Unit, Barnes-Jewish Hospital, Clinical Faculty, Washington University School of Medicine, St. Louis, MO, USA

J.J. Patel, M.D.

Division of Pulmonary & Critical Care Medicine, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226, USA



Liver disease broadly includes any disorder that disrupts the normal functions of the liver and may be categorized as acute or chronic. Due to the impressive functional reserve and regenerative capacity of this organ, it is thought that up to 75% of liver tissue must be injured before physiologic manifestations occur.

Acute liver failure (ALF) is precipitated by the destruction of a large proportion of hepatocytes, resulting in deteriorating hepatic synthetic function (jaundice, elevated prothrombin time/international normalized ratio (INR)  $\geq 1.5$ , and hypoalbuminemia) with hepatic encephalopathy (HE) in a patient without cirrhosis or preexisting liver disease [1]. Acute liver failure (ALF) is also referred to as fulminant hepatic failure, acute hepatic necrosis, fulminant hepatic necrosis, and fulminant hepatitis. A duration of illness of less than 26 weeks is commonly used to differentiate between acute and chronic liver failure. Further classification into hyperacute ( $<7$  days), acute (7–21 days), or subacute (21 days to 26 weeks) failure is associated with prognosis but more importantly reflects the underlying cause, which is the true determinant of prognosis. For example, patients with hyperacute liver failure often due to acetaminophen toxicity or ischemic causes have a better prognosis than those with subacute liver failure (e.g., Wilson's disease) [2].

Cirrhosis is a hallmark of chronic liver disease and represents a late stage of progressive hepatic fibrosis. In a cirrhotic liver, hepatic architecture is distorted and regenerative nodules are present. While early cirrhosis due to some etiologies may be treated to curtail progression, advanced stages are generally considered irreversible with the only option for treatment being transplantation. In developed countries, common causes of cirrhosis include: chronic viral hepatitis (hepatitis B, C), alcoholic liver disease, hemochromatosis, and nonalcoholic fatty liver disease (NAFLD) [3].

The increase in prevalence of chronic liver disease can be mainly attributed to an epidemic of hepatitis C virus (HCV) and NASH. It is reported that 130–150 million people globally are chronically infected with HCV [4]. A significant number of these individuals progress to cirrhosis or hepatocellular carcinoma. Although there is currently no vaccine for HCV, antiviral medication can successfully cure 90% of HCV infections, and vaccine research is ongoing.

It is estimated that 65% of Americans are overweight or obese. Obesity continues to increase and future estimates are staggering. These patients are at risk for developing metabolic syndrome. Several definitions of this disease exist, all of which share the common traits of abdominal obesity, elevated triglycerides ( $\geq 150$  mg/dL), reduced high-density lipoprotein (HDL) levels ( $<40$ – $50$  mg/dL), elevated blood pressure ( $\geq 130/85$  mmHg), elevated fasting plasma glucose ( $\geq 100$  mg/dL), or treatment for any of these (Table 14.1) [5]. Typically, the presence of 2–3 of these traits is necessary for a diagnosis of metabolic syndrome. NAFLD is the hepatic

**Table 14.1** Criteria for metabolic syndrome

Trait	Value	Comments
Abdominal obesity (waist circumference)	$\geq 102$ cm or $\geq 88$ cm	Men and women
Triglycerides	$\geq 150$ mg/dL	Or drug treatment
HDL	$<40$ mg/dL or $<50$ mg/dL	Men and women; or drug treatment
Blood pressure	$\geq 130/85$ mmHg	Or drug treatment
Fasting plasma glucose	$\geq 100$ mg/dL	Or drug treatment

manifestation of metabolic syndrome, and progression to advanced fibrosis is more likely in patients with risk factors such as older age, diabetes mellitus, body mass index (BMI)  $\geq 28$  kg/m<sup>2</sup>, higher visceral adiposity, and the presence of elevated serum aminotransferases ( $\geq 2$  times upper limit of normal) [6].

## 14.2 Nutritional Aspects of Liver Disease

All patients with liver disease should undergo nutritional assessment, but patients with advanced liver disease are at greater risk for malnutrition. Severe acute malnutrition (SAM) has been described in 50–100% of patients with decompensated liver cirrhosis (DLC) and in as many as 20% with compensated cirrhosis [7].

### 14.2.1 Pathogenesis of Malnutrition

The pathogenesis of malnutrition in cirrhosis is multifactorial. Contributing factors include: anorexia due to altered taste and smell, nausea and vomiting, diarrhea and malabsorption, poor food availability/quality (e.g., sodium-restriction), metabolic disturbances, and complications of liver disease. Malabsorption and maldigestion can result from bile salt deficiency, bacterial overgrowth, altered motility such as delayed gastric emptying or small bowel dysmotility, and increased intestinal permeability. Complications of cirrhosis such as upper gastrointestinal bleeding and portal systemic encephalopathy may also contribute to malabsorption.

The liver plays a key role in protein, carbohydrate, and lipid metabolism. Lipid metabolism is affected by decreased intraluminal bile salt concentrations, bacterial overgrowth, or associated pancreatic or intestinal disease. Glycogen stores are impaired in patients with advanced liver disease and increased amino acid turnover for gluconeogenesis can affect lean muscle mass. This can lead to starvation within a few hours of fasting. Yamauchi et al. demonstrated that late evening snacks prevented nocturnal amino acid breakdown for gluconeogenesis and improved nitrogen balance [8, 9].



Sarcopenia is common in liver disease. In patients listed for transplantation, 41% were sarcopenic. One-year survival was significantly lower in the sarcopenic versus non-sarcopenic group (49.7 vs. 87%). Sarcopenia was the single greatest predictor of mortality even when factoring INR and bilirubin [10, 11]. Decreased glycogen levels during fasting result in increased lipid/muscle oxidation, which contributes to muscle wasting in patients with liver disease. Additional mechanisms responsible for muscle wasting include cholestasis and loss of fat-soluble vitamins and decreased concentrations of bile salts. Abnormal eating habits including irregular feeding (“gorging”) were reported in 40% of patients. This in turn leads to an increase in periods of catabolism [7].

### 14.3 Nutrition Screening and Assessment

Patients with liver disease are a heterogeneous population ranging from ambulatory chronic patients to ALF patients within the intensive care unit. One cannot assume that all of these patients have SAM, however as previously stated, those with SAM have a higher morbidity and mortality, as well as a decreased quality of life than their well-nourished counterparts [7, 12]. The goal amongst practitioners in all settings should be to recognize those patients with existing SAM or at high risk of developing SAM so that timely intervention can be undertaken. A nutrition screen is the first step toward recognizing patients who require nutrition therapy and may be performed by any member of the healthcare team. A nutrition assessment is a more comprehensive evaluation of the patient’s current nutrition status and effect of disease severity and medical treatments to determine a patient specific nutrition care plan, this should be completed by a registered dietitian or other nutrition expert.

#### 14.3.1 Nutrition Screening

Numerous general nutrition screening tools exist; however, these have not been validated for use specifically in patients with liver failure. One of the most common, the Subjective Global Assessment (SGA) is easy to use, but relies heavily on subjective information. The SGA has been shown to detect SAM and predict outcomes in patients post liver transplant but underestimates the presence of SAM in patients with cirrhosis or chronic hepatitis B or C [13–15]. A single center three-phase validation study of a nutrition-screening tool for use in ambulatory patients with cirrhosis was shown to have a positive predictive value of 93%, with an approximate 75% sensitivity and specificity when compared to the dietitian’s finding of SAM by assessment. The tool consists of six questions focusing on oral intake, weight change, fat

loss, muscle wasting, peripheral edema and functional status [16]. The screening tool was developed to recognize the criteria established by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and the Academy of Nutrition and Dietetics to diagnose severe acute or chronic malnutrition [17]. Although this tool shows promise for use in patients with chronic liver failure, only 22 patients were included in the final phase of the study. Validation with a multi-center trial is still needed.

Recent guidelines for nutrition support in critically ill patients suggest that level of nutrition risk (a combination of baseline nutrition status and assessment of disease severity) should be determined for patients in whom volitional intake is anticipated to be insufficient [18]. The NRS-2002 and NUTRIC scoring systems exist to determine nutrition risk in critically ill patients [18–20]. Prospective trials have demonstrated patients with a high nutrition risk score are more likely to gain benefit (reduced nosocomial infection, total complications, and mortality) from timely nutrition intervention than patients at low risk [21, 22]. Studies specific to patients with acute liver failure need to be completed to determine the applicability in this patient population.

#### 14.3.2 Nutrition Assessment

A complete nutrition assessment is made up of several components including: medical and social history, patient/family interview for diet and weight history, biochemical data, anthropometrics and a nutrition focused physical exam (NFPE). In patients with compensated liver disease these techniques are still applicable, but interpretation may be challenging. As stated in the introduction, the role of the liver in nutrient metabolism is vast and encompasses both macro- (oxidation of amino acids, gluconeogenesis, hydrolysis of triglycerides, etc.) and micronutrients (storage and site of enzymatic steps in activation), making it difficult to discern what proportion of the abnormal findings are a result of malnutrition versus declining liver function [23]. This is why traditional serum protein markers (albumin, prealbumin, transferrin, retinol-binding protein) should not be used to represent nutrition status when performing a nutrition assessment, as they are reflection of liver function during the acute phase response. Although not useful as markers of nutrition assessment, since the synthesis of albumin and pre-albumin decrease as liver disease worsens, they may be used as prognostic markers of disease severity.

The diet history and patient/family interview provides information regarding recent intake of macro- and micronutrients, diet understanding and compliance, and frequency and chronicity of gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation). A nutrition focused physical exam (NFPE) assesses musculature, fat stores, body habitus,

presence of edema and ascites, oral cavity, skin, hair, nails and temperature. In patients with excessive fluid retention, muscle wasting may be most evident in the temporal, clavicular and scapular regions. During the interview, information regarding change in weight status should also be obtained. In the patient with hepatic failure this may provide more information regarding fluid shifts than change in muscle and fat stores. For this reason, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) nutrition guidelines for critically ill patients suggest that a dry weight or ideal body weight be used when determining energy and protein needs in liver failure patients [18].

### 14.3.3 Estimation of Needs

Energy and protein requirements for patients with liver failure are similar to other chronic and acutely ill patients. In stable, compensated patients goal energy requirements are in the range of 25–35 kcal/kg/day based on an estimated dry weight [24, 25]. Those with SAM may require up to 45 kcal/kg/day. In critically ill patients with a body mass index (BMI) in the 30–50 range 11–14 kcal/kg/day should be provided. If BMI > 50, use 22–25 kcal/kg ideal body weight/day [18]. Any patient at risk of refeeding syndrome should be progressed to goal over several days. Care should be taken to avoid overfeeding, which increases fat synthesis and increases risk of steatosis.

Cirrhotic patients are often glucose intolerant or have frank diabetes. Glucose should not be given in doses higher than 5–6 g/kg/day, especially when providing parenteral nutrition [24]. Blood glucose checks should be monitored as necessary. These patients may also have some degree of impaired fat metabolism as previously discussed. In patients with steatorrhea, fat should be restricted to no more than 25% of total calories [7].

The European Society of Parenteral and Enteral Nutrition, set a target protein intake of 1.2–1.5 g/kg/day in patients with cirrhosis [26]. Other guidelines recommend a requirement similar to other patients based on diagnosis and current treatments (e.g. renal replacement therapy) for a protein range of 1.2–2.5 g/kg/day [18]. All current guidelines recommend against protein restriction which was used historically to decrease hepatic encephalopathy which ironically results in increased muscle tissue breakdown and decreased ammonia removal [27, 28]. In addition, use of branched-chain amino acids (BCAA) in place of aromatic amino acids (AAA) has not been found to improve mental status or coma grade in patients already receiving first-line therapy (antibiotics and lactulose) [29, 30].

A retrospective study of 630 cirrhotic patients awaiting liver transplant evaluated the baseline level of protein intake,

predictors of protein intake and whether or not level of protein intake was an independent risk factor for clinical outcomes [31]. Goal intake was >1.2 g/kg/day, utilizing a dry weight for calculation. Protein intake was categorized as very low <0.8 g/kg/day (N = 162), low 0.8–1.2 g/kg/day (N = 317) and adequate >1.2 g/kg/day (N = 151). Very low protein intake was an independent predictor of SAM. In addition, 12-month mortality stratified by protein ingestion was 27.8% in the <0.8 g/kg/day, 15.9% in the 0.8–1.2 g/kg/day and 17.2% in the >1.2 g/kg/day. Of the 213 patients who remained on the transplant waiting list, a very low protein intake was associated with a 70% increase in the RR of death at 95% CI: 1.8 (1.2–2.7) [31]. It must be highlighted this study demonstrated a high prevalence of patients (76%) receiving less protein than prescribed with 26% ingesting less than recommended for healthy adults. Efforts to overcome barriers to delivery of energy and protein should be incorporated if a problem exists.

### 14.3.4 Micronutrients

Micronutrient deficiencies may occur in liver failure due to decreased oral intake, alcoholism, malabsorption, decreased hepatic storage and altered hepatic synthesis of carrier proteins. Water-soluble vitamins, specifically pyridoxine, thiamine and folic acid and trace elements zinc and selenium are most likely to be deficient in individuals with chronic alcohol-related liver disease. The most common deficiencies in non-alcoholic liver failure are often associated with fat malabsorption and include the fat-soluble vitamins A, D, E and K.

Deficiencies of water-soluble B vitamins and vitamin C may manifest as physical findings in or around the oral cavity as angular stomatitis, cheilosis, glossitis, and/or bleeding gums. More severe deficiencies may lead to neurological disorders such as ataxia and confusion. The most common concern related to thiamin deficiency is the potential for Wernicke's encephalopathy, which is most common in alcoholics, but may be seen in chronic liver failure regardless of the cause. Any patient with chronic liver failure who presents with altered mental status should receive thiamin supplementation, as it is difficult to distinguish between Wernicke's and hepatic encephalopathy [32]. Treatment for thiamin deficiency includes 1000–1500 mg thiamine within the first 24 h of treatment followed by 500 mg per day  $\times$  72 h [33].

In a blinded randomized trial a prevalence of 62.4% of vitamin A deficiency was found in patients with chronic liver disease based on serum retinol levels, plasma retinol-binding protein concentration and liver vitamin A stores [34]. The authors noted a progressive decline in serum retinol with increasing disease severity, which has been reported by other investigators as well [35, 36]. NFPE findings of vitamin A

deficiency include bitot's spot, dry eyes and perifollicular hyperkeratosis.

Suboptimal vitamin D stores are common in both cholestatic and noncholestatic liver disease [37]. In a prospective cohort study of 251 patients with cirrhosis, investigators found low serum 25(OH)D<sub>3</sub> levels were associated with advanced liver disease, increased infectious complications and mortality [38]. Vitamin D deficiency is associated with osteopenia and osteoporosis that may lead to osteomalacia. NFPE findings include rickets and muscle weakness.

Less data is available on liver failure associated vitamin E and K deficiency. One early study reported nearly 50% of cirrhotic patients suffer from vitamin E deficiency [39]. Improvement in serum aminotransferase levels and fibrosis scores have been shown with vitamin E supplementation in NASH [40, 41]. Findings of neuropathy on NFPE may be associated with vitamin E deficiency. The most common sign of deficiency of vitamin K is bleeding, it may also lead to elevated serum alkaline phosphatase and bilirubin levels [42]. Abnormal prothrombin time or finding of purpura on NFPE in patients with cirrhosis should prompt consideration of vitamin K supplementation.

Zinc deficiency may lead to alterations in taste, anorexia, skin rash, poor wound healing and altered immune function. Deficiency may be a result of fecal and urine losses combined with poor intake. Serum zinc is bound to serum albumin, which generally decreases in end-stage liver disease. Thus, investigators have proposed the use of serum zinc levels to estimate the severity of liver disease, as well as, the need for dietary intervention [43]. However, more work needs to be done to confirm the validity of this use.

A multivitamin should be considered in all patients with liver failure, given the potential for poor diet quality. Megadoses of nutrients should be reserved for those patients with clinical manifestations or biochemical data to support a deficiency.

---

## 14.4 Nutrition Delivery

### 14.4.1 Oral Diet

Cirrhotic patients may benefit from 4–6 small frequent meals for several reasons. Due to their limited liver glycogen storage capacity, a prolonged fasting time will lead to increased use of muscle glycogen, free fatty acid oxidation and production of ketones [44]. This milieu of events may accelerate loss of muscle mass. Frequent feeding may slow rate of muscle loss, as well as aiding in the prevention of hypoglycemia or hyperglycemia. Patients with ascites may complain of early satiety and have an overall increased intake with frequent feedings and smaller portion sizes. The feedings should be high protein, restricting overall sodium to

≤2000 mg per day in the presence of ascites or edema. Skipping of meals should be avoided. Concentrated oral supplements or protein modular may be needed to meet the patient's estimated energy and protein requirements [45, 46].

### 14.4.2 Enteral Nutrition

Enteral nutrition (EN) is preferred over parenteral nutrition for liver failure patients with a functional GI tract who are unable to maintain volitional feeding [18]. A review of EN in chronic liver disease discussed the lack of supporting evidence of improved clinical outcomes with the provision of EN [47]. The review suggests timing of EN earlier in the disease process with active participation of the patient in the decision to initiate EN may lead to improved outcomes. As discussed earlier, patients identified at "high nutrition risk" may demonstrate greater benefit. If the decision is made to start EN, some consideration should be given to "how" the feeds will be delivered. There continues to be debate regarding the safety of placement of a nasenteric feeding tube in a patient with esophageal varices, especially when non-banded with a recent history of bleeding. If long-term feeding is needed a percutaneous endoscopic gastrostomy (PEG) is considered standard care. However, PEGs are generally contraindicated in patients with moderate to severe ascites due to the risk of peritonitis or puncture of varices [48, 49]. In addition, these patients may have a delay in PEG tract closure, leading to potential development of a gastric fistula. Patients should be evaluated on a case by case basis for potential contraindications prior to placement of an enteral feeding device [47].

If EN is initiated a standard polymeric formula should be considered as a first choice. These products are available in various concentrations when fluid restriction is necessary. In those patients with severe malabsorption a semi-elemental or partially hydrolyzed formula may be optimal. These are available in various concentrations as well. Specialized liver disease formulas with an increased concentration of BCAAs to AAAs are very costly and should only be considered for use in patients with ESLD with hepatic encephalopathy that is refractory to baseline treatment with antibiotics and lactulose [18]. Regardless of the formula chosen, if the protein content does not provide 1.2 g/kg/day within the prescribed amount, protein modulars should be used.

### 14.4.3 Parenteral Nutrition

In patients with a non-functioning GI tract or inability to obtain EN access, initiation of parenteral nutrition (PN) should be initiated as soon as possible in those patients found to be at high nutrition risk using the NRS 2002 or NUTRIC

score. However, start of PN should be delayed in patients with septic shock regardless of their nutrition risk level. In low risk patients start of PN can be delayed 7–10 days [18]. The availability of n-3 fatty acid lipid emulsions worldwide offers a product with the potential to provide an anti-inflammatory effect. The safety and efficacy of PN containing n-3 fatty acid based lipids on cirrhotic patients with liver cancer post-operatively was studied in a RCT [50]. In a trial of 312 cirrhotic patients who underwent hepatectomy, a significant reduction of infectious complications ( $p = 0.014$ ), hospital stay ( $p = 0.018$ ) with a decrease in mortality ( $p = 0.21$ ) was realized when compared to PN containing n-6 fatty acids. Similar findings were noted in a RCT of 66 patients undergoing liver transplant. Those who received the n-3 containing PN versus the n-6 had a decrease in infectious complications, hospital length of stay and 1-year mortality. A significant improvement in liver injury was noted by a decrease of alanine aminotransferase and prothrombin time on post-transplant day 9 in the n-3 fatty acid group [51]. Repeated efforts should be made to transition the patient to EN or an oral diet when the GI tract is once again functioning.

#### 14.4.4 Branched Chain Amino Acids

Branched chain amino acids (BCAA) are amino acids which contain an aliphatic side-chain and include leucine, isoleucine, and valine. BCAA are essential amino acids, meaning they cannot be synthesized *de novo* and must be supplied via diet. As stated earlier, up to 80% of patients with DLC have pre-existing SAM and may be deficient in BCAA while patients with ALF generally do not have SAM. Dietary BCAA supplementation has been tested for prevention and management of HE. The pathogenesis of HE is complex and multi-factorial. One pathway for HE involves enterocyte oxidation of glutamine (GLN), which yields ammonia ( $\text{NH}_3$ ). In DLC and ALF, where the liver is unable to detoxify  $\text{NH}_3$  due to impaired ureagenesis,  $\text{NH}_3$  enters systemic circulation where it is able to cross the blood brain barrier and cause astrocyte swelling. A second pathway contributing to HE is related to the aromatic amino acids (AAA). AAA can only be oxidized by the liver. With DLC, AAA oxidation is reduced and plasma AAA levels are elevated. The Fischer ratio describes the ratio of BCAA to AAA (BCAA/AAA) and is normally in the range of 3–3.5. A low Fischer ratio suggests reduced BCAA and/or increased AAA. Increased AAAs out-compete the low BCAA for entry into the central nervous system, where they are metabolized into “false neurotransmitters” such as serotonin, phenylethanolamine, and octopamine [52]. BCAAs activate GLN synthesis in skeletal muscle by converting glutamate into GLN (and thus removing  $\text{NH}_3$  from circulation) and compete with AAA for CNS

entry, thus limiting HE. There are no randomized controlled trials of BCAA in DLC for prevention or treatment of HE. Of the available evidence, a meta-analysis of 16 randomized controlled trials has not demonstrated benefit of BCAA supplementation in liver cirrhosis for HE treatment [53]. The 16 studies did not include critically-ill patients, included a mixture of oral and intravenous BCAA supplementation, included varying doses of BCAA, and studied patients with mild to overt HE [53]. Even though BCAA supplementation can enhance skeletal muscle  $\text{NH}_3$  detoxification, the produced GLN travels to enterocytes, where it is oxidized to alpha-ketoglutarate, liberating two  $\text{NH}_3$ . Thus, for each  $\text{NH}_3$  detoxified by the BCAA pathway, two are produced by enterocyte GLN oxidation. BCAA may have benefit in DLC presenting as variceal hemorrhage. Variceal hemorrhage increases the gut protein load. Hemoglobin is a poor source of protein, contains valine and leucine, but is devoid of isoleucine. The BCAA imbalance that occurs as a consequence of hemoglobin degradation leads to BCAA antagonism, which enhances skeletal muscle valine and leucine metabolism, further reducing BCAA concentration in DLC. During a simulated gastrointestinal bleed in cirrhotic patients, Olde-Domink et al. demonstrated the reduced isoleucine deficiency enhanced BCAA metabolism, but when intravenous isoleucine was infused during a simulated bleed, BCAA levels increased, suggesting a possible therapeutic role for intravenous isoleucine in DLC with variceal bleed [54]. The authors did not report a clinical outcome associated with intravenous isoleucine and further data are needed before widespread implementation.

In ALF, BCAA may be low or high, depending on the stage of disease [52]. In early ALF, BCAA may be elevated due to hepatic necrosis leading to spill-over into circulation. In later stages, BCAA concentration may be low due to consequences of proteolysis and an acquired SAM. Animal studies suggest benefit of BCAA in ALF; however, there are no human data for use of BCAA in ALF [55–58]. A survey conducted from 33 centers across 11 European countries suggested BCAA were being used with high frequency for ALF (despite lack of literature support) [59]. Twenty-three of 33 centers used an AA solution containing BCAA in ALF [59]. The 2009 ESPEN Nutrition Support guidelines support BCAA use in DLC with grade III–IV HE and the 2016 ASPEN/SCCM Nutrition Support guideline recommend against BCAA use in DLC [26, 60]. The 2015 Canadian Critical Care Nutrition Support guideline suggests there is insufficient evidence for BCAA.

#### 14.5 Patient Scenario

**Question:** What protein dose and formulation should be used in this patient with acute liver failure?



**Scenario:** A 50-year old man with acetaminophen overdose is admitted to the ICU. He is confused. His blood pressure is 90/50 mmHg, has a heart rate of 120 beats per minute, and respiratory rate of 24/min. He is jaundiced, has right upper quadrant pain, is confused, and has asterixis. He is intubated for airway protection. During rounds, the resident asks if we should limit protein intake to branched chain amino acids.

**Answer:** Protein delivered enterally using a standard formula at a dose of 1.2–2.0 g/kg body weight/day is recommended. The use of a specialty (i.e. branched chain amino acid formula) is not recommended for routine use in patients with acute liver failure.

**Rationale:** ALF is hallmarked by hepatocellular necrosis, which heightens inflammation and induces a catabolic state culminating in proteolysis. Therefore, recommendations for protein are the same for other ICU patients, at 1.2–2.0 g/kg/day. BCAA depletion may reduce the Fischer ratio. The increase in aromatic amino acids (due to liver failure) outcompetes the depleted BCAA for entry into the central nervous system and contributes to hepatic encephalopathy. Trials for BCAA in ALF are lacking. Furthermore, BCAA concentrations may be low or high in ALF, depending on the stage of disease. 2016 ASPEN/SCCM guideline does not endorse routine use in patients with ALF [61].

## 14.6 Sarcopenia

Sarcopenia is loss of skeletal muscle and is common in liver disease. Forty-one percent of cirrhotics listed for transplantation were sarcopenic. One-year survival was significantly lower in the sarcopenic versus non-sarcopenic group (49.7 vs. 87%). Sarcopenia was the single greatest predictor of mortality even when factoring INR and bilirubin [10, 11]. Decreased glycogen levels during fasting result in increased lipid/muscle oxidation, which contributes to muscle wasting in patients with liver disease. Additional mechanisms responsible for muscle wasting include cholestasis and loss of fat-soluble vitamins and decreased concentrations of bile salts. Abnormal eating habits including irregular feeding (“gorging”) were reported in 40% of patients. This in turn leads to an increase in periods of catabolism [7].

Sarcopenic obesity is also prevalent in these patients and is described as a loss of lean muscle mass and simultaneous gain of adipose tissue. There are several tools such as the D’Amico stage classification, Child-Pugh, and MELD scores used to predict mortality; however, they all lack nutritional and functional status assessment. Quantifying proportion of muscle mass using computed tomography (CT) and magnetic resonance imaging (MRI) may be more reliable than subjective nutritional assessments to identify loss of muscle mass.

Englesbe et al., analyzed measurements of cross-sectional area of the psoas muscles on CT scans of 163 liver transplant patients. Correcting for donor and recipient characteristics, 1-year survival for the quartile with the smallest psoas area was worse (49.7% vs. 87.0%,  $p = 0.0001$ ) compared with the largest psoas area quartile. This relationship was also true at 3 years (26.4% and 77.2%,  $p < 0.0001$ ) [10]. Interestingly, the association between psoas area and survival was stronger than all other covariates including international normalized ration (INR) and serum bilirubin.

Therapeutic options for undernutrition and sarcopenia in cirrhotics include increased protein intake which has been demonstrated to be safe, well-tolerated, and beneficial. Other strategies as further described in the patient scenario include late-evening snacks, repeated snacks, and protein supplementation [8, 9, 62]. Some evidence suggests a role for leucine-rich supplements in the management of muscle wasting in cirrhosis. Leucine is one amino acid essential for protein synthesis and activation of anabolic signaling via the mammalian target of rapamycin (mTOR) through an undefined mechanism and as an amino acid [63, 64].

Regimented exercise including aerobic and resistance activity important for muscle metabolism. Patients with cirrhosis have reduced exercise capacity and physical activity. The potential risk of even moderate exercise can augment portal pressure and lead to variceal bleeding [65]. Therefore, patients who are able and willing to enter an exercise program may benefit from pharmacologic prophylaxis such as propranolol pretreatment [66].

Another interesting approach in cirrhotic sarcopenia is the use of transjugular intrahepatic portosystemic shunt (TIPS). The effects of TIPS on metabolism and body composition are not well defined. Several proposed mechanisms include TIPS-induced metabolic changes and increased plasma free fatty acids [67]. Additionally, portal hypertension increases enteric mucosal permeability promoting bacterial translocation. This leads to diffusion of lipopolysaccharide (LPS) and other pro-inflammatory mediators, ultimately leading to insulin resistance, a catabolic effect, and loss of protein mass. TIPS can help reduce portal hypertension and improve insulin resistance and potentially reverse sarcopenia. However, refractory sarcopenia after TIPS is associated with higher mortality [68]. Other novel treatments which require more rigorous investigation include myostatin antagonists; myostatin levels in patients undergoing transplant evaluation were significantly higher than normal controls and animal studies have shown safe myostatin expression reversal without adverse liver consequences [69, 70].

Finally, not all studies have demonstrated that sarcopenia increases mortality after liver transplantation [71]. This will be further discussed in the organ transplantation section below.



## 14.7 Patient Scenario

**Question:** What is the most appropriate meal recommendation to optimize nutrition for an outpatient with chronic liver disease?

**Scenario:** A 65-year old Caucasian male with chronic liver disease is seen in consultation for weight loss, progressive weakness, and confusion in the morning per spouse. The patient believes he is eating adequately. He presents for advice in maintaining or gaining weight and improving functional status especially in the morning.

**Answer:** You start the patient on three meals per day with three snacks per day including a late evening and early morning snack. With this regimen, the patient gains weight, feels better, and notes improvement in strength and mentation over the next 6 months.

**Rationale:** In patients with cirrhosis and chronic liver disease, there is increased protein turnover, impaired protein synthesis, and decreased hepatic glycogen stores. A late evening snack is an intervention to reduce the postabsorptive (fasting) phase and reverse anabolic resistance and sarcopenia in patients with cirrhosis [72].

## 14.8 Organ Transplant

Patients who undergo an orthotopic liver transplant (OLT) are a unique subset of patients. In the immediate post-operative phase of care, body cell mass (given in pounds and as a percentage of body weight of all the living metabolically active tissue in the body-muscle, organ, blood cells, intracellular water, proteins, and solids) is unchanged. Additionally, total body water decreases, fat content increases, and there is increased protein turnover that occurs up to 2 weeks postoperatively and beyond. There is unchanged basal energy expenditure and no further requirements for zinc and vitamin A supplementation with a functioning graft. Initiation of EN within 12 h of transplant has been shown to be safe and most patients who do not suffer an immediate postoperative complication may be able to transition to an oral diet within 5 days [73]. Early EN has been shown to decrease viral infections and reduce nitrogen turnover [74]. Immune-enhancing diets in this group of patients is controversial. Plank et al., assessed the safety of an immune-enhancing diet in patients undergoing liver transplant. Fifteen patients were given oral specialty Immunonutrition formula for a median of 54 days (range 10–168) pre-transplant and an enteral special Immunonutrition formula early after transplant. The authors suggested that Impact may have a role in improving preoperative nutritional status, speeding recovery after transplant, and reducing postoperative infections [75].

### 14.8.1 Sarcopenia and Liver Transplant

Sarcopenia is associated with increased mortality in cirrhosis; however, its impact after OLT is controversial. Investigators in one study found that median survival after liver transplant with sarcopenia compared to transplant without sarcopenia ( $115 \pm 25$  months vs.  $146 \pm 34$ ,  $p = 0.2$ ) was no different. Some differences to explain the controversy include a non-protocol CT performed in the post-transplant period likely for sicker patients who required diagnostic imaging who then had a higher risk of death and different techniques used for muscle assessment including a difference in psoas levels used (L4 vs L3) and area of muscle used in determining the final cross-sectional area [10, 71, 76]. The same authors who showed no increase in mortality in sarcopenic OLT patients did show longer hospitalizations for the sarcopenic group. In a subanalysis, they also showed 20% of transplanted patients had resolution of sarcopenia.

Sarcopenia affects quality of life, survival, and the development of complications in cirrhosis. The physiologic changes including the presence of ascites influences other indirect nutritional assessment methods (e.g., bio impedance analysis) making them inaccurate. The use of cross-sectional imaging studies to quantify skeletal muscle mass is an emerging objective and reliable nutritional assessment tool for identification of sarcopenia and preoperative nutritional/metabolic adequacy.

### Conclusions

Providing nutritional therapy in patients with liver disease is a challenging practice that requires consideration of the diverse clinical presentation of these patients from acute hepatitis to DLC in need of organ transplantation. Despite these challenges, principles of nutritional assessment and general guidelines regarding energy assessment, protein therapy, and micronutrient replacement has been shown to improve infectious morbidity, hospital length of stay, and decrease mortality even after organ transplant. Special protein and immune-enhancing formulations may be beneficial in specific conditions. In addition, the use of body composition measurement via CT or MRI to identify sarcopenia is expanding our nutritional assessment toolbox. Therefore, practitioners who address nutrition therapy are uniquely positioned to optimize outcomes for patients with liver disease.

## 14.9 Test Your Knowledge Questions

1. In patients with hepatic encephalopathy (HE), current protein guidelines recommend?
  - (a) 1.2–1.5 g/kg/day
  - (b) Use of branch-chain amino acids in all patients at risk for HE

- (c) 0.8–1.0 g/kg/day
  - (d) Provide no protein until HE resolves
  - (e) None of the above
2. Fat-soluble vitamin deficiency (vitamins A, D, E, and K) are a result of which mechanism in patients with liver disease?
- (a) Bacterial overgrowth
  - (b) Gastrointestinal bleeding complications
  - (c) Impaired glycogen storage
  - (d) **Impaired fat absorption**
  - (e) Diarrhea
3. Omega-3 fatty acid based lipids in cirrhotic patients who undergo surgery has been shown to
- (a) Increase infectious complications
  - (b) Have no change on hospital length of stay
  - (c) Decrease mortality
  - (d) **Significantly reduce infectious complications**
  - (e) None of the above

**Conflict of Interest** The authors declare no conflicts of interest with respect to authorship or publication of this manuscript.

## References

1. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American association for the study of liver diseases position paper on acute liver failure 2011. *Hepatology*. 2012;55(3):965–7.
2. <http://www.aasld.org/practiceguidelines/documents/AcuteLiverFailureUpdate2011.pdf>.
3. Heidebaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: Part I. Diagnosis and evaluation. *Am Fam Physician*. 2006;74(5):756–62.
4. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;385(9963):117–71.
5. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation*. 2009;120(16):1640–5.
6. Ratzliff V, Giral P, Charlotte F, et al. Liver fibrosis in overweight patients. *Gastroenterology*. 2000;118(6):1117–23.
7. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol*. 2012;10(2):117–25.
8. Yamauchi M, Takeda K, Sakamoto K, Ohata M, Toda G. Effect of oral branched chain amino acid supplementation in the late evening on the nutritional state of patients with liver cirrhosis. *Hepatol Res*. 2001;21(3):199–204.
9. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. *Hepatology*. 2008;48(2):557–66.
10. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg*. 2010;211(2):271–8.
11. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl*. 2012;18(10):1209–16.
12. Purnak T, Yilmaz Y. Liver disease and malnutrition. *Best Pract Res Clin Gastroenterol*. 2013;27(4):619–29.
13. Alvares-da-Silva MR, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. *Nutrition*. 2005;21(2):113–7.
14. Menta PL, Correia MI, Vidigal PV, Silva LD, Teixeira R. Nutrition status of patients with chronic hepatitis B or C. *Nutr Clin Pract*. 2015;30(2):290–6.
15. Yosry A, Omran D, Said M, Fouad W, Fekry O. Impact of nutritional status of Egyptian patients with end-stage liver disease on their outcomes after living donor liver transplantation. *J Dig Dis*. 2014;15(6):321–6.
16. Booi AN, Menendez J, Norton HJ, Anderson WE, Ellis AC. Validation of a screening tool to identify undernutrition in ambulatory patients with liver cirrhosis. *Nutr Clin Pract*. 2015;30(5):683–9.
17. White JV, Guenter P, Jensen G, et al. Consensus statement of the academy of nutrition and dietetics/American society for parenteral and enteral nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Acad Nutr Diet*. 2012;112(5):730–8.
18. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). *Crit Care Med*. 2016;44(2):390–438.
19. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321–36.
20. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care*. 2011;15(6):R268.
21. Jie B, Jiang ZM, Nolan MT, Zhu SN, Yu K, Kondrup J. Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk. *Nutrition*. 2012;28(10):1022–7.
22. Heyland DK, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally ‘at-risk’ critically ill patient: results of an international, multicenter, prospective study. *Clin Nutr*. 2015;34(4):659–66.
23. Koretz RL. The evidence for the use of nutritional support in liver disease. *Curr Opin Gastroenterol*. 2014;30(2):208–14.
24. Mueller CM. The American society for parenteral and enteral nutrition (A.S.P.E.N.) adult nutrition support core curriculum. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012.
25. Cresci GA, Chaudhary A. Nutrition for the critically ill patient with hepatic failure. In: Cresci G, editor. *Nutrition support for the critically ill patient*. Boca Raton, FL: CRC Press Taylor & Francis Group; 2005. p. 505–18.
26. Plauth M, Cabre E, Riggio O, et al. ESPEN guidelines on enteral nutrition: liver disease. *Clin Nutr*. 2006;25(2):285–94.
27. Bemeur C, Desjardins P, Butterworth RF. Role of nutrition in the management of hepatic encephalopathy in end-stage liver failure. *J Nutr Metab*. 2010;2010:489823.
28. Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol*. 2004;41(1):38–43.

29. Charlton M. Branched-chain amino acid enriched supplements as therapy for liver disease. *J Nutr*. 2006;136(1 Suppl):295S–8S.
30. Holecek M. Branched-chain amino acids and ammonia metabolism in liver disease: therapeutic implications. *Nutrition*. 2013;29(10):1186–91.
31. Ney M, Abraldes JG, Ma M, et al. Insufficient protein intake is associated with increased mortality in 630 patients with cirrhosis awaiting liver transplantation. *Nutr Clin Pract*. 2015;30(4):530–6.
32. Butterworth RF. Thiamine deficiency-related brain dysfunction in chronic liver failure. *Metab Brain Dis*. 2009;24(1):189–96.
33. Flannery AH, Adkins DA, Cook AM. Unpeeling the evidence for the banana bag: evidence-based recommendations for the management of alcohol-associated vitamin and electrolyte deficiencies in the ICU. *Crit Care Med*. 2016;44(8):1545–52.
34. Chaves GV, Peres WA, Goncalves JC, Ramalho A. Vitamin A and retinol-binding protein deficiency among chronic liver disease patients. *Nutrition*. 2015;31(5):664–8.
35. Peres WA, Chaves GV, Goncalves JC, Ramalho A, Coelho HS. Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. *Br J Nutr*. 2011;106(11):1724–31.
36. Newsome PN, Beldan I, Moussa Y, et al. Low serum retinol levels are associated with hepatocellular carcinoma in patients with chronic liver disease. *Aliment Pharmacol Ther*. 2000;14(10):1295–301.
37. Pappa HM, Bern E, Kamin D, Grand RJ. Vitamin D status in gastrointestinal and liver disease. *Curr Opin Gastroenterol*. 2008;24(2):176–83.
38. Finkelmeier F, Kronenberger B, Zeuzem S, Piiper A, Waidmann O. Low 25-hydroxyvitamin D levels are associated with infections and mortality in patients with cirrhosis. *PLoS One*. 2015;10(6):e0132119.
39. Look MP, Reichel C, von Falkenhausen M, et al. Vitamin E status in patients with liver cirrhosis: normal or deficient? *Metabolism*. 1999;48(1):86–91.
40. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2003;98(11):2485–90.
41. Sanyal AJ, Mofrad PS, Contos MJ, et al. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2004;2(12):1107–15.
42. Kowdley KV, Emond MJ, Sadowski JA, Kaplan MM. Plasma vitamin K1 level is decreased in primary biliary cirrhosis. *Am J Gastroenterol*. 1997;92(11):2059–61.
43. Friedrich K, Baumann C, Brune M, et al. Association of serum zinc levels with liver function and survival in patients awaiting liver transplantation. *Langenbeck's Arch Surg*. 2015;400(7):805–11.
44. Tsiaousi ET, Hatzitolios AI, Trygonis SK, Savopoulos CG. Malnutrition in end stage liver disease: recommendations and nutritional support. *J Gastroenterol Hepatol*. 2008;23(4):527–33.
45. Johnson TM, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. *Nutr Clin Pract*. 2013;28(1):15–29.
46. Juakiem W, Torres DM, Harrison SA. Nutrition in cirrhosis and chronic liver disease. *Clin Liver Dis*. 2014;18(1):179–90.
47. Hasse JM, DiCecco SR. Enteral nutrition in chronic liver disease: translating evidence into practice. *Nutr Clin Pract*. 2015;30(4):474–87.
48. Baltz JG, Argo CK, Al-Osaimi AM, Northup PG. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. *Gastrointest Endosc*. 2010;72(5):1072–5.
49. Yarze JC. Peritonitis after PEG placement in patients with cirrhotic ascites. *Gastrointest Endosc*. 2011;73(5):1071. author reply 1071–2
50. Zhang B, Wei G, Li R, et al. N-3 fatty acid-based parenteral nutrition improves postoperative recovery for cirrhotic patients with liver cancer: a randomized controlled clinical trial. *Clin Nutr*. 2017;36(5):1239–44.
51. Zhu XH, Wu YF, Qiu YD, Jiang CP, Ding YT. Liver-protecting effects of omega-3 fish oil lipid emulsion in liver transplantation. *World J Gastroenterol*. 2012;18(42):6141–7.
52. Holecek M. Ammonia and amino acid profiles in liver cirrhosis: effects of variables leading to hepatic encephalopathy. *Nutrition*. 2015;31(1):14–20.
53. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2015;(9):CD001939.
54. Olde Damink SW, Jalan R, Deutz NE, et al. Isoleucine infusion during “simulated” upper gastrointestinal bleeding improves liver and muscle protein synthesis in cirrhotic patients. *Hepatology*. 2007;45(3):560–8.
55. Watanabe A, Shiota T, Takei N, Fujiwara M, Nagashima H. Ammonia detoxification by accelerated oxidation of branched chain amino acids in brains of acute hepatic failure rats. *Biochem Med Metab Biol*. 1986;35(3):367–75.
56. Usui H, Ukida M, Nagashima H. Metabolism of branched-chain amino acids in rats with acute hepatic failure: a tracer study using <sup>15</sup>N-leucine. *Acta Med Okayama*. 1985;39(5):397–406.
57. Takei N. Branched chain amino acid transaminase and branched chain alpha-ketoacid dehydrogenase activity in the brain, liver and skeletal muscle of acute hepatic failure rats. *Acta Med Okayama*. 1985;39(1):1–10.
58. Horowitz ME, Schafer DF, Molnar P, et al. Increased blood-brain transfer in a rabbit model of acute liver failure. *Gastroenterology*. 1983;84(5 Pt 1):1003–11.
59. Schutz T, Bechstein WO, Neuhaus P, Lochs H, Plauth M. Clinical practice of nutrition in acute liver failure—a European survey. *Clin Nutr*. 2004;23(5):975–82.
60. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and american society for parenteral and enteral nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159–211.
61. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutr Clin Pract*. 2014;29(1):29–43.
62. Vaisman N, Katzman H, Carmiel-Haggai M, Lusthaus M, Niv E. Breakfast improves cognitive function in cirrhotic patients with cognitive impairment. *Am J Clin Nutr*. 2010;92(1):137–40.
63. Drummond MJ, Rasmussen BB. Leucine-enriched nutrients and the regulation of mammalian target of rapamycin signalling and human skeletal muscle protein synthesis. *Curr Opin Clin Nutr Metab Care*. 2008;11(3):222–6.
64. Dreyer HC, Drummond MJ, Pennings B, et al. Leucine-enriched essential amino acid and carbohydrate ingestion following resistance exercise enhances mTOR signaling and protein synthesis in human muscle. *Am J Physiol Endocrinol Metab*. 2008;294(2):E392–400.
65. Garcia-Pagan JC, Santos C, Barbera JA, et al. Physical exercise increases portal pressure in patients with cirrhosis and portal hypertension. *Gastroenterology*. 1996;111(5):1300–6.
66. Bandi JC, Garcia-Pagan JC, Escorsell A, et al. Effects of propranolol on the hepatic hemodynamic response to physical exercise in patients with cirrhosis. *Hepatology*. 1998;28(3):677–82.
67. Montomoli J, Holland-Fischer P, Bianchi G, et al. Body composition changes after transjugular intrahepatic portosystemic shunt in patients with cirrhosis. *World J Gastroenterol*. 2010;16(3):348–53.
68. Tsien C, Shah SN, McCullough AJ, Dasarthy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. *Eur J Gastroenterol Hepatol*. 2013;25(1):85–93.
69. Garcia PS, Cabbabe A, Kambadur R, Nicholas G, Csete M. Brief reports: Elevated myostatin levels in patients with liver disease: a potential contributor to skeletal muscle wasting. *Anesth Analg*. 2010;111(3):707–9.

70. Dasarathy S, McCullough AJ, Muc S, et al. Sarcopenia associated with portosystemic shunting is reversed by follistatin. *J Hepatol.* 2011;54(5):915–21.
71. Montano-Loza A, Meza-Junco J, Beaumont C, et al. Muscle wasting is not associated with higher mortality after liver transplantation. *Hepatology.* 2012;56(Suppl):651A.
72. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol.* 2012;27(3):430–41.
73. Kaido T, Ogawa K, Fujimoto Y, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. *Am J Transplant.* 2013;13(6):1549–56.
74. Kaido T, Mori A, Oike F, et al. Impact of pretransplant nutritional status in patients undergoing liver transplantation. *Hepato-Gastroenterology.* 2010;57(104):1489–92.
75. Plank LD, McCall JL, Gane EJ, et al. Pre- and postoperative immunonutrition in patients undergoing liver transplantation: a pilot study of safety and efficacy. *Clin Nutr.* 2005;24(2):288–96.
76. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol (1985).* 2004;97(6):2333–8.



Michael G. Ison and Madeleine Heldman

## Abstract

Bacterial infections are the most significant infectious source of morbidity and mortality in cirrhotic patients. Bacteria infections result in both acute decompensation in chronic liver disease and mortality in patients with decompensated cirrhosis. Spontaneous bacterial peritonitis (SBP), bacteremia, pneumonia, urinary tract infections (UTI) and skin and soft tissue infection (SSTI) are the most significant sources of infection in cirrhosis. Bacterial infections can precipitate renal failure and worsening hepatic encephalopathy, and patients with sepsis and liver disease have higher rates of acute respiratory distress syndrome (ARDS) and coagulopathy.

## Keywords

Spontaneous bacteria peritonitis • Hepatitis • Urinary tract infection • Influenza

## Learning Objectives

- Understand the impact of bacterial infections on cirrhosis.
- Discuss the pathophysiologic mechanisms that put patients with cirrhosis at risk for bacterial infections.
- Discuss the presentation, diagnosis, management and prevention of spontaneous bacterial peritonitis (SBP).
- Describe the microbiology of bacteria associated with blood stream infections, pneumonia, skin and soft tissue infection (SSTI), and urinary tract infections in patients with chronic liver disease.

Bacterial infections are the most significant infectious source of morbidity and mortality in cirrhotic patients. At least one-third

of hospitalized patients with cirrhosis will have a bacterial infection compared with less than 10% of otherwise healthy hospitalized patients [1–3]. Bacterial infections continue to be the leading cause of both acute decompensation in chronic liver disease and mortality in patients with decompensated cirrhosis, accounting for 30–50% of deaths [2, 4, 5]. Spontaneous bacterial peritonitis (SBP), bacteremia, pneumonia, urinary tract infections (UTI) and skin and soft tissue infection (SSTI) are the most significant sources of infection in cirrhosis. While recognition and treatment of SBP has decreased mortality from 80% to 20% in the past 30 years, mortality from infections, particularly pneumonia and septicemia, remain quite high [1]. Bacterial infections can precipitate renal failure and worsening hepatic encephalopathy, and patients with sepsis and liver disease have higher rates of acute respiratory distress syndrome (ARDS) and coagulopathy compared to patients with sepsis and no underlying liver disease [6, 7].

M.G. Ison, M.D., M.S., F.I.D.S.A., F.A.S.T. (✉)  
Divisions of Infectious Diseases and Organ Transplantation,  
Northwestern University Feinberg School of Medicine,  
Chicago, IL 60611, USA

Transplant and Immunocompromised Host Infectious Diseases  
Service, Northwestern University Comprehensive Transplant  
Center, Chicago, IL 60611, USA  
e-mail: [mgison@northwestern.edu](mailto:mgison@northwestern.edu)

M. Heldman, M.D.  
Department of Internal Medicine, Northwestern University  
Feinberg School of Medicine, Chicago, IL 60611, USA  
e-mail: [madeleine.heldman@northwestern.edu](mailto:madeleine.heldman@northwestern.edu)

## 15.1 Pathophysiology of Bacterial Infection Risk in Cirrhosis

Historically, bacterial infections in patients with liver disease are primarily due to translocation of native gut bacteria complicated by immune dysregulation. In healthy persons, low-grade bacterial translocation occurs regularly, as bacteria

travel to the liver through mesenteric lymph nodes and the portal venous system. The reticuloendothelial system of the liver, comprised of Kupffer cells, exert a filtering effect, inhibiting bacteria from reaching the systemic circulation [1, 6–9]. Animal models suggest that both damage to Kupffer cells as well as septal and sinusoidal fibrosis increase risk of bloodstream infections (BSI) and SBP [8]. Small bowel bacterial overgrowth and decreased intestinal motility in cirrhosis also contribute to bacterial translocation from the gut [7]. Proton-pump inhibitors, commonly prescribed for gastrointestinal bleeding in cirrhosis, alter the microbiome and appear to facilitate bacterial translocation as well [1, 9, 10].

Cirrhosis-associated immunodeficiency (CAID) describes the array of immunodeficiency present in cirrhosis that lead to the evolution of infections. The healthy liver produces complement proteins and Protein C, which play critical roles in the adaptive immune system's effector response. Production of these key proteins are reduced in patients with cirrhosis [2, 7]. Splenomegaly leads to sequestration of circulating monocytes, neutrophils, and lymphocytes and further impairs cellular immunity [6]. Impaired phagocytosis and chemotaxis also contribute to the evolution of infection in cirrhosis [2, 6–8]. Malnutrition and alcohol use, which are common in cirrhotic patients, further compromise immune function [2, 5].

The systemic response to bacterial infections in cirrhosis is profound. Since cirrhotic patients have a baseline hyperdynamic circulatory state, infection often facilitates cardiovascular collapse and places patients at high risk of septic shock. Nitric oxide, which is a primary driver of systemic vasodilation and circulatory shock, may be overexpressed in cirrhotic patients [6, 7]. Upregulation of various cytokines, including TNF- $\alpha$ , IL-1, IL-6, and IL-17, also occurs in liver disease and contributes to exaggerated responses to infection [2, 6, 8]. Lastly, since the diseased liver is less efficient at clearing bacterial endotoxins, exaggerated systemic response to bacterial infections may occur more frequently [2, 6, 7].

## 15.2 Spontaneous Bacterial Peritonitis

Spontaneous Bacterial Peritonitis (SBP) is defined as infection of ascitic fluid in the absence of an intraabdominal source [11]. It is the most frequent bacterial infection in cirrhosis and accounts for 25–31% of bacterial infections in cirrhosis [7]. The mechanism of infection involves translocation of gastrointestinal bacteria to the portal vein and mesenteric lymph nodes and spillage into ascitic fluid [10–13]. Cirrhotic ascites is a primarily transudative fluid, with low opsonic activity [12], and, as a result, bacterial growth may proceed unabated. Ten percent of cirrhotic patients with ascites will develop SBP within 1 year of diagnosis, and SBP is present in 30–50% of all hospitalized patients with cirrhosis [7]. The development of SBP also predicts mortality—1-year mortality after the first

episode of SBP is over 30% [7]. While SBP is classically associated with cirrhotic ascites, SBP is also present in patients with ascites secondary to acute liver failure [10].

### 15.2.1 Presentation

Although hypothermia is common among cirrhotic patients, fever, which may be mild, is one of the most common presenting symptoms in patients with SBP. Other symptoms include abdominal pain, increased amount of ascitic fluid, failure of diuretic treatment, new or worsening hepatic encephalopathy, and diarrhea [1, 7]. Ten to thirty percent of patients with SBP are asymptomatic [1]. The International Ascites Club recommends that SBP be considered in the following circumstances: all cirrhotic patients with ascites on admission to hospital; patients with ascites who develop signs of sepsis, hepatic encephalopathy, renal impairment or altered gastrointestinal motility; all cirrhotic patients with ascites and a gastrointestinal bleed.

### 15.2.2 Risk Factors

Risk Factors for SBP include:

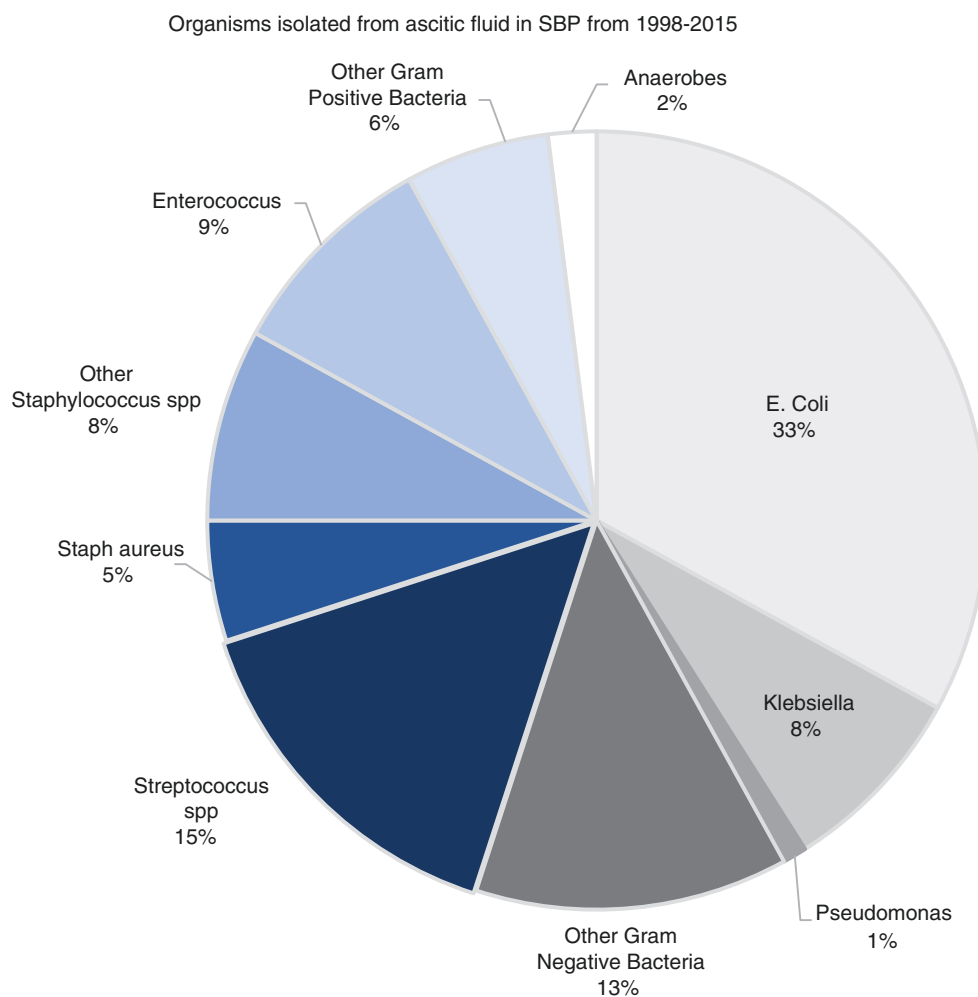
- Low ascitic fluid protein ( $<1$  g/dL) [6, 7, 10].
- Elevated serum bilirubin [6, 7, 10].
- Advanced cirrhosis: high MELD scores and Child-Pugh stage C disease [14].
- Hyponatremia (serum sodium  $<125$  mg/dL) [14].
- Variceal hemorrhage [6, 7, 10, 14].
- Use of proton-pump inhibitor (PPI) [10, 15].
- Genetic polymorphisms in TLR2 and *NOD2*, receptors which recognize bacterial [1, 3, 7, 9, 10].

Use of non-selective beta-blockers may protect against SBP, but their use may increase the risk of circulatory collapse from SBP and may decrease transplant free survival [10].

### 15.2.3 Microbiology

Historically, gram-negative bacilli have been the major cause of SBP. However, microbial patterns have shifted to include more gram-positive cocci with broader use of antibiotics and invasive procedures over the past three decades. From 1971 to 1991, *E. coli* was the most prevalent source of SBP, present in 46% of cases. Other common sources included *Streptococcus* (30%), *Klebsiella* (9%). Since 1998, *E. coli* has remained the most common organism associated with SBP, but now accounts for only one-third of cases [10]. Gram-positive cocci now comprise 25% of pathogens isolated in SBP, with

**Fig. 15.1** Causative organisms of spontaneous bacterial peritonitis



*Streptococcus* and *Enterococcus* being the most prevalent. Twenty-five to thirty percent of these GPC-associated SBP cases occur in patients taking fluoroquinolone prophylaxis [5, 16]. Multi-drug resistant gram-negative bacilli, including extended spectrum  $\beta$ -lactamase (ESBL) producing *E. coli*, carbapenem-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* have been isolated in cases of health-care acquired SBP [16]. *Enterococcus faecium* and methicillin-resistance staphylococcus aureus (MRSA) have also been isolated in healthcare associated SBP [5]. Anaerobes remain a rare source. Pathogens associated with cases of SBP from 1998–2015 are summarized in Fig. 15.1 [10].

#### 15.2.4 Diagnosis

Paracentesis is required to diagnose SBP. Diagnosis can be made by when either the absolute neutrophil (polymorphonuclear cell, PMN) count in the ascitic fluid is  $>250$  cell/mm<sup>3</sup> or ascitic fluid culture is positive, although careful interpretation of positive cultures with low cell counts is needed. The

absolute PMN count can be calculated by adjusting for red blood cell contamination (absolute PMN = [total WBC  $\times$  % PMNs] – [RBC/250]).

Although the gold standard for diagnosing SBP is the presence of positive ascitic fluid culture and many polymorphonuclear cells ( $>250$  cells/mm<sup>3</sup>), cultures are negative frequently (up to 40%) [10]. This is known as culture-negative neutrophilic ascites (CNNA), and is a common variant of SBP that should be treated the same as culture-positive SBP. The absence of a positive fluid culture in CNNA may reflect low pathogen burden [10, 12] and use of PCR demonstrates that bacterial DNA are present at detectable levels in most cases [17]. Blood culture bottles should be inoculated at the bedside with at least 10 mL of ascitic fluid to increase culture yield [7, 10]. When ascites fluid culture is positive, a single pathogen is isolated in 90% of cases [10]. Urinary reagent strips that assess leukocyte esterase activity should not be used to diagnose SBP due to an unacceptable low positive predictive value and high false negative rate [7, 10]. Assays of lactoferrin in ascitic fluid may be a more accurate predictor of infection [3, 7].

Infrequently, secondary bacterial peritonitis resulting from a perforated viscus may be present when spontaneous bacterial peritonitis is suspected. Polymicrobial organisms on a gram stain are indicative of secondary bacterial peritonitis. Additionally, analysis of ascitic fluid chemistry using Runyon's criteria can be used to differentiate SBP from secondary bacterial peritonitis. The presence of two or more of these criteria are 90% specific for secondary bacterial peritonitis [18]:

1. Total protein >1 g/dL
2. Glucose <50 mg/dL
3. LDH > upper limit of normal for serum

### 15.2.5 Management

Community-acquired SBP should be treated with antibiotics that cover *Enterobacteriaceae* and non-enterococcal gram-positive cocci. Intravenous antibiotics, including a third-generation cephalosporin or amoxicillin-clavulanate are recommended; IV amoxicillin-clavulanate is not available in the United States. Cefotaxime has been the most well studied, and has excellent penetration into ascitic fluid [10]. Ceftriaxone is also effective in treating SBP, though its high protein-binding activity makes it theoretically less effective in cirrhosis, where protein synthesis is impaired [10]. Oral ofloxacin and IV ciprofloxacin may also be used in uncomplicated SBP, but should be avoided in patients on fluoroquinolone prophylaxis or in geographic areas with high levels of fluoroquinolone resistance to *Enterobacteriaceae* [7, 19]. Levofloxacin may be efficacious in patients on fluoroquinolone prophylaxis who cannot tolerate  $\beta$ -lactams [10]. Treatment should be continued for 5 days, as 5 day courses of antibiotics are as efficacious but less costly than 10 day courses [6, 10, 20]. Nosocomial infections, defined as infections occurring after 48 h of hospitalization, are resistant to  $\beta$ -lactam in 33–78% of cases [5]. Meropenam or tigecycline can be used in nosocomial cases of SBP in areas with a high prevalence of ESBL-producing pathogens [3, 5, 7]. Antibiotic therapy should be tailored if culture is positive and sensitivities are available. Follow-up paracentesis 48 h after initiation of treatment is recommended in patients who do not rapidly improve [10]. A reduction in PMN count by >25% suggests appropriate antibiotic coverage; if such a reduction is not observed, antibiotics should be broadened or the possibility of secondary bacterial peritonitis should be considered [3, 7, 10].

Hepatorenal syndrome (HRS) is a common complication of infections in patients with cirrhosis, and occurs in 30–40% of cases of SBP [7]. The addition of albumin, which acts as a plasma expander, to antibiotic treatment sig-

nificantly reduces the rate of HRS [3, 7, 10]. Treatment with albumin (1.5 g/kg on day 1 followed by 1 g/kg on day 3), is particularly effective and recommended for patients at high risk of HRS, identified as having any one of the following either bilirubin >4 mg/dL or creatinine >1 mg/dL [3, 7, 10]. Albumin is not necessary in patients who are at a low risk for HRS [3, 7].

### 15.2.6 Prevention

Patients who have a primary episode of SBP have a 40–70% chance of recurrent SBP within 1 year of initial SBP presentation [10]. Long-term use of norfloxacin has been shown to decrease the recurrence of SBP and is recommended as secondary prophylaxis for patients who have one episode of SBP; unfortunately, norfloxacin is not currently widely available commercially [6, 7, 19]. Ciprofloxacin and trimethoprim-sulfamethoxazole may also be used [10]. Daily dosing is recommended to limit growth of fluoroquinolone-resistant organisms [10]. Primary prophylaxis is also used in patients with low ascitic albumin concentration and GI bleeding, as these patients are at a particularly high risk for developing SBP [2, 5–7, 10]. The antibiotic used, route of administration, and length of treatment depends upon the indication for prophylaxis as outlined in Table 15.1.

**Table 15.1** Antibiotic regimens for prophylaxis against SBP

Indication for prophylaxis	Prophylactic antibiotic regimen
History of SBP	Oral trimethoprim-sulfamethoxazole (800–160 mg) daily OR ciprofloxacin 500 mg/day OR norfloxacin <sup>a</sup> 400 mg/day
Inpatients with total ascitic fluid protein <1 g/dL and hospitalized for reasons OTHER than SBP or GI bleed	Oral trimethoprim-sulfamethoxazole (800–160 mg) daily OR oral ciprofloxacin 500 mg/day OR oral norfloxacin <sup>a</sup> 400 mg/day while hospitalized
Cirrhosis and GI hemorrhage	Child-Pugh Class A: oral trimethoprim-sulfamethoxazole (800–160 mg) twice daily OR oral norfloxacin <sup>a</sup> 400 mg daily OR oral ciprofloxacin 500 mg q12 hours OR IV ciprofloxacin 400 mg q12 hours; treat for total of 7 days Child-Pugh Class B or C: IV ceftriaxone 1 g daily; transition to oral therapy with either trimethoprim-sulfamethoxazole (800–160 mg) daily OR ciprofloxacin 500 mg q12 hours OR norfloxacin <sup>a</sup> 400 mg daily once patient can tolerate oral medication; treat for a total of 7 days

<sup>a</sup>Norfloxacin is not currently available in the United States



## 15.3 Other Bacterial Infections

### 15.3.1 Bloodstream Infections

Bloodstream infections occur in 4–21% of cirrhotic patients, and are ten times more prevalent in patients with cirrhosis than in the general population [8]. Gut translocation is the primary mechanism of bacteremia in liver disease, and bacteria that reside in the gut—gram-negative bacilli, anaerobes, and *Enterococcus*—are the primary pathogens [6–8]. In the early 2000s, health-care acquired gram-positive cocci, including MRSA, became a common source of blood stream infections. Fluoroquinolone prophylaxis and increased use of broad-spectrum antibiotics have led to emergence of multi-drug resistant (MDR) and extreme-drug resistant (XDR) gram-negative bacilli. In a single-center study of 162 cirrhotic patients with a bloodstream infection, 60% of pathogens were resistant to third-generation cephalosporins. Of the gram-negative bacilli isolated, 25% were classified as MDR and 21% were classified as XDR [21].

### 15.3.2 Endotipsitis

Endotipsitis, ongoing bacteremia in the presence of an infected thrombus or endovascular infection affecting the TIPS, has been increasingly reported over the past 10 years, with *Enterococcus* and *Staphylococcus* as the most common isolated pathogens [8, 22]. Because a TIPS cannot be removed outside of liver transplantation, diagnosis and treatment of endotipsitis is more complicated than that of infections associated with removable indwelling devices. Endotipsitis should be suspected in patients with a TIPS and bacteremia when the source of bacteremia is unknown despite evaluation for other causes. If endotipsitis is suspected, patency of the TIPS should be evaluated using Doppler ultrasound—a thrombus or vegetation is strongly suggestive of endotipsitis [22]. Treatment relies solely on the use of antibiotics, as source control with TIPS removal is not possible. There are no clear guidelines for the duration of treatment, though in case series, patients who successfully cleared their bacteremia were treated for a mean duration of 6 weeks [22]. If bacteremia is prolonged or recurs after a prolonged period of therapy, chronic suppressive therapy until transplantation should be considered. Though active infection is often a contraindication for liver transplantation, there are reports of successful clearance of endotipsitis after the device is removed during transplant [22].

### 15.3.3 Pneumonia

Bacterial pneumonia is also a significant source of morbidity and mortality in cirrhotic patients. The epidemiology of

community-acquired lower respiratory infections is the same in patients with and without liver disease with *Streptococcus pneumoniae* being the most common cause. Other common causes include oropharyngeal bacteria, including *Haemophilus influenza* and anaerobes as well as less common bacteria, including *Klebsiella*, *Legionella* and *Mycoplasma* [1, 2]. *Pseudomonas aeruginosa* is one unique bacteria that is more commonly identified in patients with liver disease than those without [23]. The severity of pneumonia in patients with chronic liver disease is enhanced with a higher rate of ICU admission, more severe clinical presentations, increased prevalence of bacteremia and increased mortality [1, 9, 23]. Pneumococcal vaccination is recommended for adults with chronic liver disease; while the 23-valent polysaccharide pneumococcal (PPSV-23) vaccine is primarily recommended for this patient population, those individuals who are being evaluated for transplantation should also receive the 13-valent pneumococcal conjugated vaccine (PCV13) [24]. Ideally, the PCV13 should be given first followed by the PPSV-23 6 months or more after the PCV13 vaccine.

### 15.3.4 Skin and Soft Tissue Infections (SSTIs)

Chronic liver disease also predisposes patients to skin and soft tissue infection. Venous insufficiency, lower extremity edema and immune dysfunction predispose chronic liver disease patients to skin infections of the lower extremity. While gram-positive cocci are the most common source of SSTIs in liver disease [1, 2], gram-negative bacilli are also relatively common in patients with liver disease compared to controls. A prospective study in India identified gram-negative bacilli as the most common isolate in cirrhosis, with male sex, alcohol use, and bare-foot walking being major risk factors [25]. *Vibrio vulnificans*, a rare, curved gram-negative bacillus found in warm seawater, can invade open wounds and cause severe hemorrhagic bullae and rapid necrotizing fasciitis. *Vibrio vulnificans* is also associated with bacteremia and septic shock after consumption of oysters grown in infected waters. In a study of over 1000 cases in Japan, 23% of patients with *Vibrio vulnificans* had underlying cirrhosis [26]. Cirrhosis due to hemochromatosis is a particularly strong risk factor for *Vibrio* infection [7].

### 15.3.5 Urinary Tract Infection (UTI)

Urinary Tract Infections are common in cirrhosis, particularly in females [2]. Bacteruria is often asymptomatic, and indwelling catheters are a significant risk factor [2]. Recurrent UTI, most often with *E. coli* is often found in patients with primary biliary cirrhosis (PBC), and to a lesser extent in autoimmune

hepatitis (AIH), even prior to diagnosis [27]. It has been hypothesized that molecular mimicry between a human and *E. coli* epitope may account for this phenomenon [27].

## 15.4 Clostridium Difficile Infection and C. difficile Associated Diarrhea (CDAD)

*Clostridium Difficile* infection resulting in diarrhea is becoming increasingly common and cirrhotic patients are more likely to contract CDAD than the general population [7, 28]. *C. difficile* is more common among hospitalized patients with liver disease than among those without liver disease; alcoholic hepatitis and autoimmune hepatitis are particularly strong risk factors for CDAD [28]. Risk factors for CDI in cirrhosis are similar to risk factors in the general population and include antibiotic use, including outpatient fluoroquinolone prophylaxis, and PPI use [7, 28, 29]. Fluoroquinolone prophylaxis for SBP use is associated with infection with the particularly virulent NAP1 strain [28]. Cirrhotic patients with CDAD have longer lengths on hospital stay and increased mortality compared with cirrhotic patients without CDAD [7, 28, 29].

### 15.4.1 Management of CDAD

Treatment of *C. difficile* in patients liver disease is similar to treatment in patients without liver disease, and depends on disease severity. CDI/CDAD severity can be divided into three categories [30]:

1. Mild to moderate, which involves with diarrhea and absence of any features of severe or severe and complicated disease.
2. Severe, which includes a serum albumin of less than 3 g/dL AND either a white blood cell count >15,000 cells/mm<sup>3</sup> OR abdominal tenderness.
3. Severe and complicated, defined as CDAD/CDI in patients with a fever >38.5 °C, WBC >35,000 cells/mm<sup>3</sup> or <2000 cells/mm<sup>3</sup>, those who require admission to an intensive care unit, have evidence of shock, including hypotension requiring vasopressors, lactate >2.2 mmol/L, altered mental status, or other end organ damage.

The first line treatment for mild to moderate CDI/CDAD consists of oral metronidazole (or IV metronidazole in patients who are unable to take medication by mouth) for 10–14 days. Oral vancomycin is traditionally reserved for cases refractory to metronidazole or for severe CDI/CDAD. Patients with severe and complicated CDI should be treated with both oral vancomycin and intravenous metronidazole [28, 30, 31]. Vancomycin can be administered rectally if ileus is present,

and surgery should be considered in severe refractory disease. Treatment with fidoximycin for recurrent CDI has been proven effective in the general population, but there is no data specific to patients with liver disease [28].

### Summary Learning Points

- Bacterial infections are the leading cause of mortality in chronic liver disease.
- Translocation of gut bacteria, particularly gram-negative bacilli, occurs frequently in cirrhosis and is the major mechanism putting this population at risk for bacterial infection.
- Cirrhosis acquired immunodeficiency (CAID) is a collection of immune system deficiencies in both innate and adaptive immunity in cirrhosis.
- Spontaneous bacterial peritonitis (SBP) is the most frequent bacterial infection seen in cirrhosis. Risk factors include advanced cirrhosis, GI bleeding, low ascitic protein count, and PPI use. All patients with cirrhosis admitted to the hospital should undergo diagnostic paracentesis regardless of reason for admission.
- SBP should be treated with a third-generation cephalosporin. Secondary prophylaxis should be given after the first episode of SBP. Primary prophylaxis should be given in patients with GI bleeds and low ascitic protein count.
- Primary bacteremia is also a significant cause of morbidity in cirrhosis. Recently, there has been an increase in prevalence of in gram-positive cocci and multi-drug or extreme-drug resistant gram-negative bacilli.
- Bacterial pneumonia can be particularly severe in cirrhosis. All patients with chronic liver disease should be vaccinated with PPSV-23.
- Skin and Soft Tissue infections (SSTIs) in cirrhosis are often due to the same gram-positive cocci that cause SSTI in healthy persons. However, cirrhosis greatly increases the risk of infection with gram-negative bacilli and the particularly virulent *Vibrio vulnificans* pathogen.
- Urinary Tract Infections are common and may be asymptomatic in cirrhosis.
- *Clostridium Difficile* associated diarrhea is more common in cirrhotic patients compared to the general population and is associated with poor outcomes in cirrhosis.

## 15.5 Viral Infections in Chronic Liver Disease

### 15.5.1 Hepatitis A Virus

Hepatitis A virus (HAV) accounts for half of all causes of viral hepatitis in the United States [32]. The illness begins with a period of nausea and anorexia and progresses to an icteric phase with jaundice and a marked elevation in bili-

rubin [33]. The disease usually resolves and rarely results in acute liver failure or death. However, the disease is significantly more severe in chronic liver disease. Patients with underlying chronic liver disease have up to a 23-fold increase in mortality compared to patients with hepatitis A and no underlying liver disease [34]. Those with underlying HCV infected with HAV have higher mortality rates and are more likely to develop acute liver failure compared with individuals with underlying HBV or no underlying viral liver disease at the time of HAV infection [32, 34, 35]. The hepatitis A vaccine is both safe and effective in patients with chronic liver disease, and it is recommended for all patients with chronic liver disease [35]. However, the vaccine is less immunogenic in patients with advanced liver disease, suggesting vaccination early after the diagnosis of liver disease [34].

### 15.5.2 Hepatitis B Virus

Hepatitis B virus can be the underlying cause of chronic liver disease or occur in individuals with underlying liver disease due to other causes. Vaccination against hepatitis B is of particular importance in patients with liver disease listed for liver transplant, as new active infection can occur post-transplant in non-immune recipients from donor livers from chronic, HBsAg-negative, carriers. Like the HAV vaccine, the HBV vaccine has good immunogenicity in mild to moderate chronic liver disease, but poor immunogenicity in end stage liver disease [34]. The impact of superimposed HBV on chronic liver disease has primarily been studied in the cohort of patients with HCV and is discussed below. However, given the severity of superimposed HBV infection, HBV vaccination is recommended in all patients with ESLD.

### 15.5.3 Hepatitis B and Hepatitis C Co-infection

Hepatitis B and C share similar risk factors and commonly occur in the same individual. Between 2 and 10% of patients with hepatitis C virus (HCV) have a detectable hepatitis B surface antigen (HBsAg) [36]. However, high sensitivity testing for HBV DNA can detect occult hepatitis B infection in up to one-third of HCV patients with undetectable HBsAg [37], suggesting the incidence of co-infection is under-recognized [36]. It is thought that HCV exerts a suppressive effect on HBV, because HBV DNA levels are relatively low in HBV/HCV coinfection compared to HBV monoinfection [36, 38]. The most common scenario in which HCV/HBV coinfection occurs is a HCV superinfection on chronic HBV infection [36]. Fulminant hepatic failure due to HCV alone is rare; however studies from areas

of where hepatitis B is endemic suggest that chronic underlying HBV at the time of acute HCV infection results in a sevenfold increase in the risk of fulminant hepatic failure [36, 39]. HBV acquisition in pre-existing hepatitis C is less common, but has been reported to result in the development of ascites and hepatic encephalopathy [36]. Coinfection of HBV/HCV results in substantially higher rates of progression to both cirrhosis and hepatocellular carcinoma compared with monoinfection with either virus [36, 38, 40].

### 15.5.4 Hepatitis D Virus

Hepatitis D virus (HDV) is an RNA virus with tropism for hepatocytes and relies on HBsAg for survival. Therefore, infection with HDV occurs only in individuals with HBV infection. Two infection patterns are observed:

1. *Co-infection* occurs in acute HBV infection when HDV infects the same individual at the same time. The course mimics acute HBV infection, though HDV co-infection is a risk factor for progression to fulminant hepatitis [41]. Because the majority of acute hepatitis B episodes are self-limited and result in disappearance of HBsAg and appearance of anti-HBsAg antibodies, HDV disappears once seroconversion occurs.
2. *Superinfection* occurs when HDV infects a chronic HBsAg-positive carrier, resulting in a particularly virulent acute hepatitis or decompensation [41]. Half of all cases of acute liver failure in HBsAg-positive individuals occurs in the presence of HDV [41]. HDV persists in 90% of cases of superinfection and leads to cirrhosis within 5–10 years in 70% of cases [41].

### 15.5.5 Hepatitis E Virus

Hepatitis E virus (HEV) causes an acute hepatitis similar to hepatitis A and is primarily found in Asia, Africa and the Middle East. Studies from endemic regions of the world suggest that HEV causes rapid decompensation in cirrhosis with mortality as high as 70% at 4 weeks post-infection [42].

### 15.5.6 Human Immunodeficiency Virus (HIV)

In the era of antiretroviral therapy, liver disease is the most common cause of death in HIV-infected individuals, accounting for 14–18% of all deaths [43]. Coinfection of HIV in chronic viral hepatitis is common.

In the United States and Europe, 30% of HIV patients are co-infected with HCV [43]. Shared risk factors include

injection drugs use and exposure to blood products. Hemophiliacs with HIV have a 60–90% risk of coinfection with HCV, and HIV positive injection drug users have a 50–90% HCV coinfection rate [44, 45]. HIV coinfection with HCV halves the likelihood of clearing HCV viremia, and accelerates the progression to cirrhosis [43, 44]. Decompensated cirrhosis is 2–6 times more common in HCV cirrhosis when HIV infection is present [43, 44]. Treatment of HIV with anti-retroviral therapy (ART) reduces, but does not completely eliminate, the impact of HIV infection on HCV disease progression [45]. Treatment of HCV with interferon/ribavirin is more effective at higher CD4 counts, and thus ART for HIV should be initiated prior to treatment of HCV with interferon/ribavirin if CD4 count is  $<500/\mu\text{L}$  [45]. New direct-acting antivirals (DAAs) for the treatment of HCV are expected to eliminate the need to elevate CD4 count prior to HCV treatment, but careful consideration of drug interactions between DAAs and ARTs is necessary when treating both infections [46].

Approximately 10% of HBV infected individuals are co-infected with HIV [43]. HIV increases the risk of developing chronic HBV infection, with a more profound effect at lower CD4 counts [43, 47]. HIV also enhances the progression to cirrhosis and increases the risk of developing hepatocellular carcinoma in HBV infection [47]. Much of the hepatocellular toxicity in hepatitis B is due to immune response against hepatic cells, which would imply that hepatocellular toxicity should be diminished when a virus causing immunodeficiency is present. Indeed, HIV/HBV coinfection results in lower alanine aminotransferase (ALT) levels compared to HBV monoinfection [47]. However, ALT levels do not correlate with clinical severity and liver biopsy is recommended to determine extent of disease [43, 47]. One mechanism of HIV-induced HBV exacerbation is that particularly virulent HBV strains are more prevalent in HIV-coinfected cases. A strain of HBV with a direct cytopathic effect, resulting from a deletion in the core/pre-core region of the HBV genome, has been shown to be more prevalent in HBV/HIV coinfection compared to HBV monoinfection [47]. HIV also induces microbial translocation, which may lead to increased immune activation and thus increased HBV-induced hepatocellular injury [47]. In general, when selecting anti-retroviral therapy (ART) for HIV treatment, agents that also have activity against HBV should be used—tenofovir plus emtricitabine or tenofovir plus lamivudine are common regimens [43, 47]. Treatment of HIV without appropriately treating HBV can rarely cause worsening of hepatitis due to immune reconstitution inflammatory syndrome (IRIS) [43, 47]. Further, interruption of HBV-active anti-retrovirals may cause an acute hepatitis B reactivation and rapid progression of liver disease.

### 15.5.7 Influenza Infection

Data regarding the effect of influenza virus in cirrhosis is largely limited to case reports. Influenza A (H3N2) was associated with three cases of decompensated cirrhosis during the 1997–1998 epidemic [48]. In a small, single-center case series, influenza A/H1N1/09 was associated with lethal ARDS and pneumonia in patients with cirrhosis [49]. Influenza vaccine has good immunogenicity in cirrhotic patients, with trends toward a reduction in influenza infection and hepatic decompensation in vaccinated cirrhotic patients [40]. Patients with cirrhosis who develop influenza infection should be treated with active therapy, including one of the neuraminidase inhibitors, oseltamivir, peramivir or zanamivir, as soon as influenza is suspected without waiting for results of testing to confirm infection.

#### Summary Learning Points

- Hepatitis A and B vaccines should be administered to all patients with chronic liver disease.
- HBV and HCV frequently co-exist and are associated with increased rates of cirrhosis compared to monoinfection with either virus.
- HIV is commonly present in individuals infected with either HBV or HCV, and increases the severity of liver disease in these patients.
- Cirrhosis predisposes to severe pulmonary complications of influenza infection. These patients should receive the influenza vaccine to prevent infection and early treatment with neuraminidase inhibitors when infection is suspected.

---

## 15.6 Infection in Acute Liver Failure

Acute liver failure (ALF) in the absence of known, pre-existing liver disease is relatively rare, with about 2000 cases per year in the United States [50], and thus is not as well studied as acute decompensation of cirrhosis. Patients with acute liver failure, like those with cirrhosis, are at an increased risk of infection due to the impaired innate immunity and exposure to indwelling lines, and up to 90% of ALF patients will develop an infection while hospitalized [50]. However, the role of gut translocation in predisposition to infection is less defined in ALF [50, 51]. Infection most commonly develops early in the hospital course, within 2–5 days of admission, but may also develop after hospital day 10 and accounts for 25% of late mortality in ALF [50]. Because active infection is a contraindication to liver transplant, which is the only curative option in advanced ALF, infection has a significant indirect effect on mortality. Identifying infection in ALF may be difficult, as leukocytosis and fever are absent in 30% of cases [50].



Bacterial infections have been documented in up to 90% of patients with ALF. Historically, gram-positive cocci due to pneumonia predominated as the leading cause of blood stream infections in ALF [50]. More recently, gram negative organisms are becoming increasingly common and now account for close to half of bacterial infections with *Klebsiella* spp. being the most common gram-negative pathogen [50]. Fungal infections, including *Candida*, *Aspergillus* and *Pneumocystis jiroveci* may also occur in ALF [50, 51], particularly when renal dysfunction is present [51], and should be considered when leukocytosis or fever persist despite broad spectrum antibiotics. Reactivation of CMV infection has also been described in ALF, particularly in patients being treated with corticosteroids for the underlying cause of acute liver failure [50].

Retrospective review of over 200 patients in a liver intensive therapy unit showed that high grade hepatic encephalopathy and SIRS criteria on hospital admission were predictive of the development of bacteremia, and bacteremia was associated with increased need for mechanical ventilation and renal replacement therapy [50, 52, 53]. Oral antibiotics with poor absorption to decontaminate the bowel was once thought to decrease incidence of bacterial infection [50], but initiation of prophylactic antibiotics, including systemic antibiotics, has not been shown to decrease 21-day mortality [50, 54]. While antimicrobial prophylaxis has been shown to increase the likelihood of transplant in ALF due to acetaminophen overdose, it does not increase survival in this group [54]. Thus, routine antimicrobial prophylaxis in ALF is not recommended [50, 55]. However, routine surveillance with chest radiographs, fungal and bacterial cultures of blood, sputum and urine is recommended given the high incidence of infection in this population [55], and antibiotics should be started at the first sign of rapid clinical deterioration, especially when worsening hepatic encephalopathy develops [55].

### Summary Learning Points

- Infection occurs in up to 90% of patients with acute liver failure.
- While routine prophylactic antibiotics is not recommended in ALF, surveillance for infection should occur regularly.
- Antibiotics should be started in the absence of documented infection in patients with rapid clinical decline and severe hepatic encephalopathy.

### References

1. Strauss E. The impact of bacterial infections on survival of patients with decompensated cirrhosis. *Ann Hepatol*. 2013;13(1):7–19.
2. Taneja SK, Dhiman RK. Prevention and management of bacterial infections in cirrhosis. *Int J Hepatol*. 2011;2011:784540.
3. Fernández J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol*. 2012;56(Suppl 1):S1–12.
4. Bar K, Wisplinghoff H, Wenzel RP, Bearman GM, Edmond MB. Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infections due to enterococci. *BMC Infect Dis*. 2006;6:145.
5. Pleguezuelo M, Benitez JM, Jurado J, Montero JL, de la Mata M. Diagnosis and management of bacterial infections in decompensated cirrhosis. *World J Hepatol*. 2013;5(1):16–25.
6. Nanchal RS, Ahmad S. Infections in liver disease. *Crit Care Clin*. 2016;32(3):411–24.
7. Bunchorntavakul C, Chamroonkul N, Chavalitdharmong D. Bacterial infections in cirrhosis: a critical review and practical guidance. *World J Hepatol*. 2016;8(6):307–21.
8. Bartoletti M, Giannella M, Lewis RE, Viale P. Bloodstream infections in patients with liver cirrhosis. *Virulence*. 2016;7(3):309–19.
9. Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. *World J Gastroenterol*. 2014;20(10):2542–54.
10. Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis—bacteriology, diagnosis, treatment, risk factors and prevention. *Aliment Pharmacol Ther*. 2015;41(11):1116–31.
11. Runyon B. Spontaneous bacterial peritonitis in adults: treatment and prophylaxis. In: Post T, ed. Up to date. Up to date, Waltham, MA. Accessed 23 July 2016.
12. Mowat C, Stanley AJ. Review article: Spontaneous bacterial peritonitis—diagnosis, treatment and prevention. *Aliment Pharmacol Ther*. 2001;15(12):1851–9.
13. Ginès P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. *N Engl J Med*. 2004;350(16):1646–54.
14. Schwabl P, Bucsecs T, Soucek K, et al. Risk factors for development of spontaneous bacterial peritonitis and subsequent mortality in cirrhotic patients with ascites. *Liver Int*. 2015;35(9):2121–8.
15. Xu HB, Wang HD, Li CH, et al. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. *Genet Mol Res*. 2015;14(3):7490–501.
16. Alexopoulou A, Papadopoulos N, Eliopoulos DG, et al. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int*. 2013;33(7):975–81.
17. Such J, Francés R, Muñoz C, et al. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, non-neutrocytic ascites. *Hepatology*. 2002;36(1):135–41.
18. Soriano G, Castellote J, Alvarez C, et al. Secondary bacterial peritonitis in cirrhosis: a retrospective study of clinical and analytical characteristics, diagnosis and management. *J Hepatol*. 2010;52(1):39–44.
19. Casper M, Mengel M, Fuhrmann C, et al. The INCA trial (impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver cirrhosis and ascites): study protocol for a randomized controlled trial. *Trials*. 2015;16:83.
20. Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology*. 1991;100(6):1737–42.
21. Bartoletti M, Giannella M, Caraceni P, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. *J Hepatol*. 2014;61(1):51–8.
22. Mizrahi M, Adar T, Shouval D, Bloom AI, Shibolet O. Endotipitis—persistent infection of transjugular intrahepatic portosystemic shunt: pathogenesis, clinical features and management. *Liver Int*. 2010;30(2):175–83.
23. Viasus D, Garcia-Vidal C, Castellote J, et al. Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. *Medicine (Baltimore)*. 2011;90(2):110–8.

24. Fakhraei H, Khalilzadeh S, Khanbabaei G, et al. Current recommendations for pneumococcal vaccination of children and adults. *Tanaffos*. 2015;14(3):161–4.
25. Sood A, Midha V, Goyal O, et al. Skin and soft tissue infections in cirrhotics: a prospective analysis of clinical presentation and factors affecting outcome. *Indian J Gastroenterol*. 2014;33(3):281–4.
26. Nagao Y, Matsuoka H, Seike M, et al. Knowledge of *Vibrio vulnificus* infection among Japanese patients with liver diseases: a prospective multicenter study. *Med Sci Monit*. 2009;15(10):PH115–20.
27. Smyk DS, Bogdanos DP, Krieser S, Billinis C, Burroughs AK, Rigopoulou EI. Urinary tract infection as a risk factor for autoimmune liver disease: from bench to bedside. *Clin Res Hepatol Gastroenterol*. 2012;36(2):110–21.
28. Trifan A, Stoica O, Stanciu C, et al. *Clostridium difficile* infection in patients with liver disease: a review. *Eur J Clin Microbiol Infect Dis*. 2015;34(12):2313–24.
29. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, et al. *Clostridium difficile* is associated with poor outcomes in patients with cirrhosis: a national and tertiary center perspective. *Am J Gastroenterol*. 2010;105(1):106–13.
30. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108(4):478–98. quiz 499
31. Leffler DA, Lamont JT. *Clostridium difficile* infection. *N Engl J Med*. 2015;373(3):287–8.
32. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med*. 1998;338(5):286–90.
33. McIntyre N. Clinical presentation of acute viral hepatitis. *Br Med Bull*. 1990;46(2):533–47.
34. Keefe EB. Hepatitis A and B superimposed on chronic liver disease: vaccine-preventable diseases. *Trans Am Clin Climatol Assoc*. 2006;117:227–37. discussion 237–8
35. Almasio PL, Amoroso P. HAV infection in chronic liver disease: a rationale for vaccination. *Vaccine*. 2003;21(19–20):2238–41.
36. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol*. 2008;23(4):512–20.
37. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med*. 1999;341(1):22–6.
38. Liu CJ, Chen PJ, Chen DS. Dual chronic hepatitis B virus and hepatitis C virus infection. *Hepatol Int*. 2009;3(4):517–25.
39. Chu CM, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. *Gut*. 1999;45(4):613–7.
40. Leise MD, Talwalkar JA. Immunizations in chronic liver disease: what should be done and what is the evidence. *Curr Gastroenterol Rep*. 2013;15(1):300.
41. Farci P, Niro GA. Clinical features of hepatitis D. *Semin Liver Dis*. 2012;32(3):228–36.
42. Kumar Acharya S, Kumar Sharma P, Singh R, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol*. 2007;46(3):387–94.
43. Price JC, Thio CL. Liver disease in the HIV-infected individual. *Clin Gastroenterol Hepatol*. 2010;8(12):1002–12.
44. Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *World J Gastroenterol*. 2009;15(8):996–1003.
45. Clausen LN, Lundbo LF, Benfield T. Hepatitis C virus infection in the human immunodeficiency virus infected patient. *World J Gastroenterol*. 2014;20(34):12132–43.
46. Panel AIGH. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62(3):932–54.
47. Thio CL, Hepatitis B. Human immunodeficiency virus coinfection. *Hepatology*. 2009;49(5 Suppl):S138–45.
48. Duchini A, Viernes ME, Nyberg LM, Hendry RM, Pockros PJ. Hepatic decompensation in patients with cirrhosis during infection with influenza A. *Arch Intern Med*. 2000;160(1):113–5.
49. Marzano A, Marengo A, Ruggiero T, et al. Clinical impact of A/H1N1/09 influenza in patients with cirrhosis: experience from a nosocomial cluster of infection. *J Med Virol*. 2013;85(1):1–7.
50. Donnelly MC, Hayes PC, Simpson KJ. Role of inflammation and infection in the pathogenesis of human acute liver failure: clinical implications for monitoring and therapy. *World J Gastroenterol*. 2016;22(26):5958–70.
51. Craig DG, Lee A, Hayes PC, Simpson KJ. Review article: the current management of acute liver failure. *Aliment Pharmacol Ther*. 2010;31(3):345–58.
52. Karvellas CJ, Pink F, McPhail M, et al. Predictors of bacteraemia and mortality in patients with acute liver failure. *Intensive Care Med*. 2009;35(8):1390–6.
53. Arai M, Kanda T, Yasui S, et al. Opportunistic infection in patients with acute liver failure. *Hepatol Int*. 2014;8(2):233–9.
54. Karvellas CJ, Cavazos J, Battenhouse H, et al. Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. *Clin Gastroenterol Hepatol*. 2014;12(11):1942–1949.e1941.
55. Lee WMLA, Stravitz RT. AASLD position paper: the management of acute liver failure: update. 2011.

Tessa W. Damm, Gaurav Dagar, and David J. Kramer

## Abstract

Liver dysfunction may manifest during systemic illness as a consequence of circulatory compromise — inadequate perfusion, passive congestion, intrahepatic redistribution of blood flow — or as a consequence of hepatocellular or fixed tissue macrophage (Kupffer cell) cytotoxicity. It is probable that hepatic dysfunction exacerbates the hemodynamic sequelae and multisystem dysfunction which results from infection. Certainly, underlying hepatocellular disease such as that caused by steatosis, viral hepatitis which results in changes to the cytoarchitecture will predispose to hepatocellular dysfunction in systemic illness. Some discrete functions of the liver can be measured. However, several key aspects related to immune function are poorly characterized. Liver dysfunction is often inferred from extra-hepatic organ dysfunction the severity of which can be quantified and used to characterize the severity of liver dysfunction.

## Keywords

Critical Illness • Liver Failure • Sepsis • Shock • Heart Failure • Respiratory Failure

## 16.1 Introduction

Critical illness presents myriad demands on and insults to the functioning liver. These include compromised hepatic blood flow, hypoxemia, endotoxemia and compromised hepatic out-flow with congestive hepatopathy. In this brief review we will address liver function and reserve in critical illness related to sepsis, shock, hypoxemia and circulatory overload. Inference is

drawn from a growing literature addressing acute on chronic liver failure and the course of critical illness in cirrhosis. However, we attempt to understand liver dysfunction that results from the insult which precipitates critical illness or from the response to that insult in the setting of a premorbid normal liver.

The clinical burden for patients with cirrhosis requiring ICU care is high—3,127,986 patients with cirrhosis are evaluated in the ED annually in the USA of whom 75% are admitted with the leading indication being infection [1]. At least 26,000 patients with cirrhosis require ICU care annually with in-hospital mortality exceeding 50% despite aggressive critical care management [2]. Such patients represent an extreme but these observations support reevaluating liver function in critically ill patients without a history of liver disease.

---

T.W. Damm, D.O.  
Aurora Critical Care Service, Aurora Health Care,  
2901 West Kinnickinnic River Parkway, Suite 315,  
Milwaukee, WI, USA

G. Dagar, M.B.B.S.  
Medical College of Wisconsin, Milwaukee, WI, USA

D.J. Kramer, M.D. (✉)  
Aurora Critical Care Service, Aurora Health Care,  
2901 West Kinnickinnic River Parkway, Suite 315,  
Milwaukee, WI, USA

School of Medicine and Public Health, University of Wisconsin,  
2901 West Kinnickinnic River Parkway, Suite 315,  
Milwaukee, WI, USA  
e-mail: [David.kramer@aurora.org](mailto:David.kramer@aurora.org)

## 16.2 Background

Standard measures of liver function reflect hepatocellular integrity (aminotransferases) as well as the integrity of the biliary system (alkaline phosphatase, gamma-glutamyl transpeptidase [GGT] and bilirubin). At steady state,

synthetic function is evident in serum protein levels, including albumin and liver-derived coagulation proteins. The latter are reflected in prothrombin time or Factor V levels. Elevations in bilirubin reflect increased pigment load, and/or impaired cellular elimination or compromised biliary drainage.

Liver dysfunction, identified early in the critically ill, portends a poor prognosis [3]. The formation of MEGX from lidocaine has been studied in critically ill patients. Survivors and non-survivors differed significantly with survivors having a significantly higher level of MEGX formed than non-survivors. These abnormalities were evident in the first 3 days of ICU care [4].

Unfortunately, there are few measures of hepatic immune function that are commercially available. Disruptions of these processes are particularly likely in the critically ill but severity must often be gauged from convention measures of liver function and clinical assessment.

Hepatic elimination of toxins and drugs depends on the interplay of hepatic blood flow and hepatocellular extraction. Intrahepatic vascular sinusoids with the adjacent space of Disse provide a large surface area for contact with the microvilli of hepatocytes to facilitate absorption. Increased hepatic venous and sinusoidal pressures resulting from increased right atrial pressure which might yield higher filtration fraction more probably interstitial edema and compromised portal flow as venous resistance rises—will result in decreased clearance.

Blood flow can be estimated at steady state using the Fick principle for compounds with high extraction ratios such as ICG. Dynamic changes may violate the assumption of steady state. After surgery, blood flow can be measured directly with vascular flow probes. In other settings, the Doppler flow velocity can be integrated over time to yield an estimate of flow. Arterial flow velocity waveform analysis allows estimation of tissue compliance from resistive and/or pulsatility indices. Hepatic compliance can be assessed with elastography (Fibroscan). In critical illness a decrease in compliance is correlated with worse outcome [5]. However, passive congestion resulting from volume overload will similarly alter transient elastography, compromising specificity.

### 16.2.1 Functional Liver Studies

Noninvasive measurements of liver function in outpatients with known liver disease, at steady state, are under development. These measures assess microsomal function (aminopyrine breath test, benzodiazepine metabolism), cytosolic function (galactose breath test or galactose elimination capacity) and mitochondrial function (arterial ketone body ratio,  $AKBR = \text{acetoacetate}/\text{betahydroxybutyrate}$  [6]; methionine breath test). However, none have been system-

atically used to assess liver function or hepatic reserve in critically ill patients. In the ICU these studies are unlikely to distinguish between the critical illness and the underlying liver function. Future refinement might permit the intensivist recognition of the patient at risk for hepatic decompensation.

Exhaled breath analysis holds more promise for screening at risk populations. Exhaled nitric oxide correlates with the severity of liver disease and the severity of hepatopulmonary syndrome [7, 8]. More recently, exhaled limonene has been recognized in exhaled breath and related to the presence of liver disease [9]. However, changes were assessed over a period of several days.

In contrast, ICG retention at 15 min (ICG-15. Normal <14%) has been studied in critically ill patients. The related plasma disappearance rates of ICG (PDRICG %/min) were higher in survivors of critical illness compared to non-survivors for the first 3 days of ICU admission. ICG clearance proved more sensitive than conventional liver function tests [10]. These observations confirm similar observations by Maynard and colleagues which were underpowered to reach statistical significance [4].

A novel approach to assess reserve comes from hepatobiliary oncologic practice where portal vein embolization (PVE) contralateral to the site of hepatocellular carcinoma is used to promote hypertrophy prior to resection of the cancer with partial hepatectomy. Diseased liver fails to hypertrophy as rapidly or completely after PVE. Hepatobiliary scintigraphy with 99m-Tc-mebrofenim has been used to gauge the liver's hepatic hypertrophic response to PVE. Such a test might uniquely gauge hepatic "reserve" [11].

### 16.2.2 Scoring Systems

Functional hepatic reserve has been characterized in terms of sequelae of dysfunction and attendant mortality. Specific scores in common use include Child Turcotte Pugh and model for end-stage liver disease (MELD). MELD is dependent upon bilirubin, INR and creatinine. However, outcome from critical illness even in a patient with cirrhosis is better predicted by acute physiology and chronic health evaluation (APACHE) or sequential organ failure assessment (SOFA) and its recent adaptation for liver disease CLIF-SOFA [12–15].

### 16.2.3 Blood Flow

Only two organs have dual blood supplies—the lung and the liver. The liver is supplied by the hepatic artery and the portal vein which arises from the confluence of the splenic and superior mesenteric veins. Although portal flow is higher than hepatic arterial flow, oxygen saturation is approximately



75% in the portal vein; so oxygen supply from each vessel is approximately equal. However, the biliary system is supplied exclusively by the hepatic artery. This balance of oxygen transport changes as hepatic arterial flow varies inversely with portal blood flow. Indeed, the liver efficiently increases oxygen extraction as blood flow and oxygen transport decrease. However, below a critical level of blood flow oxygen extraction plateaus and hepatocellular function is compromised [16].

The lobular architecture of the liver results in discreet blood flow into sinusoids from hepatic arterial and portal venous branches and outflow from the hepatic vein. The liver encases the inferior vena cava (IVC) such that hepatic venous drainage empties almost directly into the right atrium and from there to the pulmonary circulation.

Increases in right atrial pressure—whether from volume overload, heart failure, pulmonary hypertension or pericardial tamponade—result in increases in hepatic venous and sinusoidal pressures. Hepatic congestion leads to a typical pattern of LFT abnormalities including isolated hyperbilirubinemia and prolonged prothrombin time. Conversely, hypoxic and ischemic insults to the liver result in dramatic elevation of aminotransferases ( $>20 \times$  ULN) over the first 36–48 h with subsequent hyperbilirubinemia and elevation of alkaline phosphatase. The initial consequence is necrosis with mitochondrial damage and DNA fragmentation followed later by cytokines released by Kupffer cells [17].

The hepatic cellular architecture reveals intimate connection between hepatocytes and Kupffer cells—a huge population of fixed tissue (stellate) macrophages which line the walls of the sinusoids and are a key part of the mononuclear phagocytic system. These cells are activated in response to infection. Hypoxemia produces a similar response. Inflammatory mediators are released into the hepatic vein with direct impact on both the heart and the lungs which are immediately downstream.

Significant compromise of hepatocellular function may be subclinical and manifest only when the patient becomes critically ill. Hepatic morphology on imaging with MRI or computed tomography can define liver size and perfusion characteristics which provide insight into underlying liver disease such as steatosis or hepatic infiltration due to tumor or amyloid. Identification of small, shrunken, cirrhotic liver with attendant evidence of portal hypertension is particularly valuable will help guide management. However, the impact on hepatic architecture can be discerned only from liver biopsy. Recently, hepatic compliance has been assessed by transient elastography which correlates with fibrosis in several disease processes. Unfortunately, imaging is useful to define underlying hepatic pathology but not particularly helpful in understanding hepatic function or reserve with respect to critical illness.

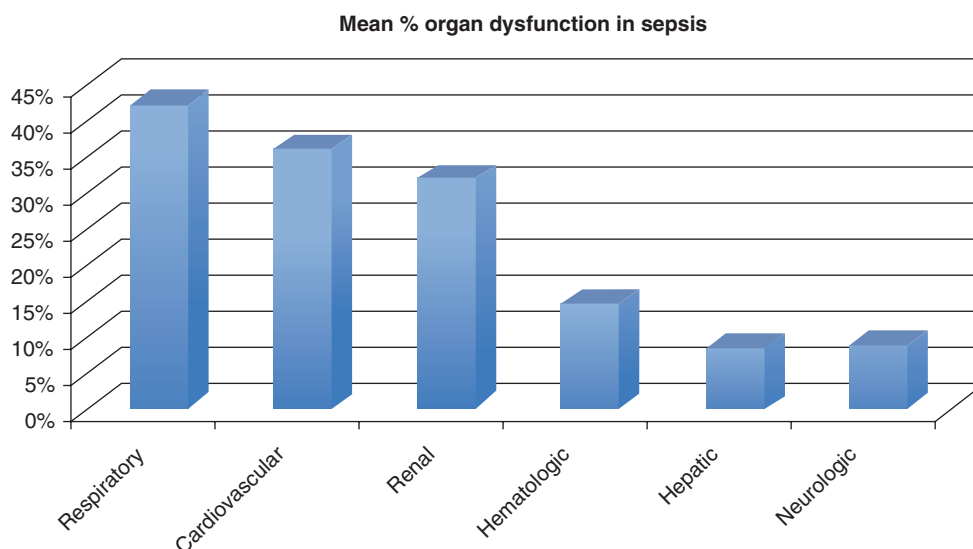
Occult liver disease and dysfunction impact survival from critical illness. Clinical history of toxin and/or viral exposure, physical exam with stigmata of chronic liver disease, biochemistry and imaging will heighten suspicion. More sophisticated analysis of liver function such as by analysis of exhaled gas, carbon-labeled breath tests, assessment of hepatic blood flow with ICG and analysis of hepatocyte enzymatic function such as cytochrome P450 are not yet routine. Liver dysfunction revealed by such methods is associated with increased morbidity and mortality in critical illness even when standard evaluation of the liver is normal. Even in the research setting, calibration is crude and timeframe for assessment much longer than is relevant for managing critical illness.

Hypoxic hepatitis overlaps with ischemic hepatitis and is evidenced by severe aminotransferase elevation ( $20 \times$  upper level of normal) which occurs in approximately 10% of the critically ill [18]. Liver injury results in release of inflammatory mediators. The hepatic vein drains into the upper inferior vena cava almost directly into the right heart and pulmonary circulation with the common sequela of lung injury and ARDS. Not only is mortality resulting from infection higher in the setting of acute liver injury, acute lung injury is both more common and more severe [19].

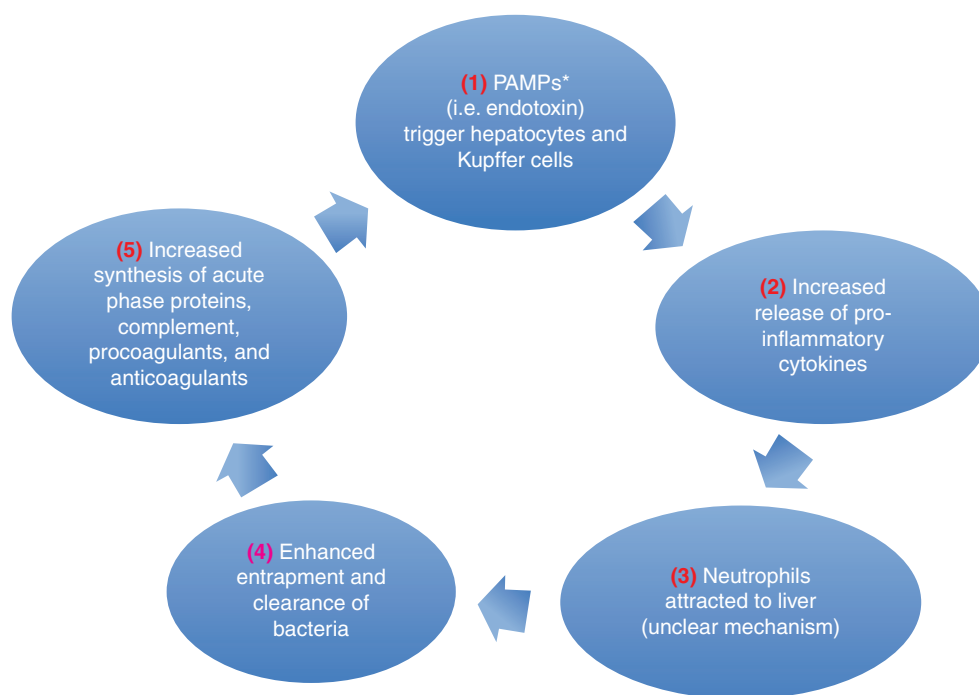
In the absence of sophisticated testing, serum bilirubin is a reasonable reflection of liver function in the critically ill. Of course, the differential diagnosis for hyperbilirubinemia includes biliary obstruction, associated with elevation of the alkaline phosphatase and hemolysis which increases indirect, unconjugated bilirubin. The incidence of liver dysfunction in critically illness varies widely in the literature because of different thresholds. Highly restrictive definitions, such as Angus and colleagues use, suggest an incidence of 1.3% [20]. However, using the SOFA thresholds of 6 mg/dL and 12 mg/dL for SOFA 3 (liver dysfunction) and 4 (liver failure) respectively, the Epidemiology of Sepsis Study (EPISEPSIS) reported an incidence of 47% and 6% respectively [21]. Similar findings are evident from the PROWESS study of Protein C in sepsis: 36% for liver dysfunction and 3% for liver failure [22].

Cholestasis that develops with sepsis, is unconjugated, intrahepatic (unrelated to bile duct obstruction) and reflects disrupted cytoarchitecture and disordered bile excretion and transport. Infection is the etiology in approximately 20% of jaundice evaluated in the community hospital setting [23]. Multiple factors may cause hemolysis (bacterial and fungal toxins, medications, etc.) and so increase pigment load. Conjugation is not compromised but bile transport into the canaliculi requires energy and is considered the rate-limiting step. Consequently, hepatic ischemia and hypoxia are likely to impact this step [24]. Furthermore, cytokines such as TNF alpha and IL-1 beta are released by the Kupffer cell in response to endotoxin (lipopolysaccharide) and further depress bile acid transport [25]. A downward spiral may

**Fig. 16.1** Organ dysfunction and failure amongst patients with sepsis. Liver dysfunction occurs in a minority of patients with sepsis. When it does occur, however, it is a marker of poor prognosis particularly amongst patients with associated jaundice. Percentages of incidence above are taken from compiled data published by Yan et al. [27]



**Fig. 16.2** The cascade of hepatocellular events that occur in response to systemic infection. The same response that targets resolution of infection, if unbalanced, leads to hepatic dysfunction [24, 29]. (Asterisk) PAMPs Pathogen Associated Molecular Patterns



be envisioned in which a paucity of bile acids results in villous atrophy of the intestine which leads to translocation and additional infectious burden to the liver.

## 16.3 Sepsis and the Liver

### 16.3.1 Introduction

Sepsis is the leading cause of mortality in intensive care units worldwide. By definition, sepsis is a condition of life-threatening organ dysfunction caused by a dysregulated host

response to infection [26]. It is logical that as the largest immune organ in the body, there will be a relation between liver function and patient outcome in the setting of sepsis. Liver dysfunction that occurs as a result of sepsis is an independent marker of increased mortality. Moreover, pre-existing liver dysfunction is a risk factor for the progression of any infection to sepsis. As such, the liver not only serves a key function in the host immune response to sepsis, but also the presence of pre-existing dysfunction is known to exacerbate sepsis severity [27].

Liver dysfunction and failure occurs in 8.5% patients with sepsis, a lower frequency than other organ dysfunction (see

Fig. 16.1) [27]. Although the incidence of liver dysfunction due to sepsis (incidence of 34.7%) is less than other organ dysfunction, it portends a significantly more grave prognosis [28]. Hyperbilirubinemia is the most commonly observed laboratory abnormality signaling hepatic dysfunction in sepsis. This often occurs with only modest concomitant elevations in alkaline phosphatase and transaminases [29] (Fig. 16.2).

### 16.3.2 Pattern of Injury

Hepatic failure has traditionally been considered a late manifestation of septic shock. As more information is elucidated germane to the classification of sepsis-associated liver injury, however, it is clear that a majority of hepatic injury is actually of onset within the first 24 h of an episode of sepsis [28]. Such insults to the liver occur early in the pathogenesis of sepsis, likely due to the compounding effects of hypoperfusion and inflammatory change.

Patterns of injury to the liver in sepsis are broadly categorized as hypoxic hepatitis (including shock liver and hepatocellular injury) and cholestasis with jaundice. Nitric oxide (NO) plays a critical role in microvascular circulatory homeostasis of the liver and is up-regulated in hepatocytes and Kupffer cells during sepsis augmenting both local and systemic vasodilation [29]. Hepatic hypoperfusion results from both arterial vasodilation with splanchnic pooling and an insufficient cardiac output relative to the degree of vasodilation and afterload reduction. Resultant hepatic mitochondrial injury is marked by aminotransferase leak. If the physiologic processes causing septic shock are reversed (infection controlled and hemodynamics return to normal) liver injury will resolve. Despite improvement in LFTs, the patient may remain hyperbilirubinemic and have reduced lactate clearance and protein synthesis with impaired gluconeogenesis. Rarely, hypoxic hepatitis may progress to fulminant hepatic failure [30].

In contrast, jaundice is often a late event in the course of sepsis and thought to be a response of supra normal tissue perfusion that causes intrahepatic cholestasis. This secondary dysfunction occurs when Kupffer cells are activated by pathogen-associated molecular patterns (PAMPs) such as endotoxin and release reactive oxygen products, tissue necrosis factor- $\alpha$ , interleukin (IL)-1, and IL-12 [28]. Increased inflammatory cytokines contribute to sinusoidal dilatation, congestion and occlusion that in turn contribute to hepatocellular injury in addition to increasing mesenteric venous pressure and congestion which creates the appropriate milieu for translocation of gut flora [29]. When jaundice is present (defined as total bilirubin level  $> 3.0$  mg/dL) as a result of sepsis, the proportion of patients with poor outcome is 68.6% which compares poorly to 45.5% in patients with no sepsis-associated liver dysfunction who are without jaundice [28].

Regardless of category, liver dysfunction in sepsis is believed to be the sequelae of microcirculatory disturbances, a pro-inflammatory state, and immunosuppression. Therefore any type of infection in the setting of sepsis may result in hepatic impairment. It is the balance of the liver's natural response or lack thereof that regulates systemic response and determines patient outcome. Interestingly, autopsy studies of patients who succumb to sepsis almost universally show hepatitis and liver steatosis, confirming the crucial role of the liver in one's response to sepsis [27].

Intra-abdominal infections leading to gram-negative bacteremia are most commonly associated with jaundice, though again any infection resulting in sepsis may result in hepatic impairment. Histologically, the most common hepatic findings secondary to sepsis are bland intra-hepatic cholestasis with Kupffer cell hyperplasia and reactive hepatitis. Ongoing research, however, has identified organism-specific patterns of histologic hepatic change. Such patterns have been identified for gram-negative and gram-positive infections both of abdominal and extra-abdominal etiology [29].

## 16.4 Management and Further Research

Currently there are no specific treatments recommended to mitigate sepsis-associated hepatic injury other than the overarching recommendations included in the surviving sepsis guidelines targeting end-organ support. Such recommendations include but are not limited to maintenance of hemodynamic flow to minimize organ hypoperfusion and concurrent antimicrobial and other indicated adjunct interventions required for infectious source control [31].

Recent clinical studies have prompted renewed interest in the role of intravenous ascorbic acid (vitamin C) as a treatment for sepsis. Low circulating levels of vitamin C are characteristic and nearly universal in patients with acute critical illness [32]. As humans are incapable of intrinsic ascorbic acid synthesis, intravenous supplementation is necessary in the reversal of this deficiency. Doses of 6 g daily (administered in divided doses of 1.5 g every 6 h for 4 days) when administered together with intravenous hydrocortisone and thiamine have preliminarily been associated with a reduction of duration of vasopressor requirement, organ dysfunction, and mortality from severe sepsis and septic shock [33].

The antioxidant vitamin C functions as a scavenger of free oxygen radicals, which restores other cellular antioxidants which down-regulates hepatic production of inflammatory mediators. This in turn preserves or restores endothelial integrity, function and microcirculatory flow [34] such that the progression of sepsis to shock and multiple organ dysfunction syndrome (MODS) is attenuated. Unquestionably this will represent an ongoing area of research in how to

specifically abate the multifaceted hepatic response and injury in sepsis.

The role of adrenal function in sepsis-induced cholestasis is also unclear. As noted in Nessler's review [35] (see Table 16.1) an improvement in the hepatic component of the SOFA score is evident in the steroid treated arm of CORTICUS [36]. Furthermore, corticosteroids may directly modulate cytokine-induced bile transport dysfunction [37]. Certainly, adrenal insufficiency is often recognized in liver failure [38, 39].

Intensive insulin therapy (IIT) has fallen out of favor [40] as the risk of harm seems to outweigh any putative benefit. However, subsequent analysis of the University of Leuven data demonstrates a reduction in biliary sludge, assessed sonographically, a reduction in cholestasis and a decreased incidence of ischemic hepatitis in the patients randomized to IIT [41]. Correlates for cholestasis included acuity (high APACHE-II), diagnosis of gastrointestinal or hematologic abnormality, requirement for vasopressor support with norepinephrine and parenteral nutrition. The authors speculate that IIT exerts an anti-inflammatory effect at the level of the biliary epithelium.

N-acetylcysteine modulates ischemic hepatitis [42] and modifies ischemia/reperfusion injury to bile ducts in livers recovered from non-heart-beating donors (DCD) [43]. However, when used in ARDS, acute renal failure, septic shock a mortality benefit cannot be demonstrated. It would be of interest to see if early administration to critically ill patients at risk for liver injury might have selective benefit.

Liver support devices such as the molecular adsorbent recirculation system (MARS) do not improve survival in acute on chronic liver failure. However, MARS consistently reduces bilirubin and improves the hemodynamics of acute

on chronic liver failure [44]. A trial of MARS in cholestasis of sepsis or ischemic hepatitis would be welcome.

## 16.5 The Liver in Cardiac Disease

Heart failure is a clinical syndrome characterized by the inability of the systemic perfusion to meet the body's metabolic demand. It is usually caused by cardiac pump dysfunction, systolic or diastolic. Dysfunction of either the left or the right ventricle can affect the liver. The most common cause of right ventricular dysfunction (and pulmonary hypertension) is cardiac dysfunction of the left side (systolic and diastolic dysfunction of the left ventricle), or left sided valve disease (aortic and mitral valve).

Cardiac dysfunction can affect the liver in two ways: Passive congestion (congestive hepatopathy) and ischemic hepatitis.

### 16.5.1 Passive Congestion

Passive congestion of the liver is usually caused by right ventricular (RV) dysfunction through elevated right atrial (RA) pressure leading to increased venous pressure and congestion of the liver and its capsule.

In the liver, hepatocytes can be divided into three zones based on their proximity to the portal triad, through which the blood and oxygen delivery takes place. Periportal hepatocytes are closest to the portal triad, followed by mid-zonal and then centrilobular hepatocytes which are farthest away from the oxygen source. Therefore centrilobular hepatocytes are affected earliest in patients with cardiac dysfunction. This type of liver injury was classified as Grade A by Sherlock et al. In Grade B and Grade C, heart failure persists and cell necrosis extends outwards towards the portal triads. In Grade A hepatocyte necrosis, the reticulin pattern is essentially normal. In the next stage there is reticulin condensation in the centrilobular region due to loss of cells from this region. This is followed by centrilobular reticulin proliferation, with actual production of new reticulin. Collagen is also increased in the centrilobular region. Fibrous tissue extends outwards but does not reach the periphery of the lobule. This leads to reversal of lobular pattern, giving the appearance of portal tracts lying centrally, which is classical for cardiac cirrhosis. Portal tracts remain unaffected. In long standing cases the portal tracts can also become involved, bile ducts proliferate, and fibroblasts are seen. This can lead to a mixed picture and at this point cardiac cirrhosis may be difficult to differentiate from portal cirrhosis [45].

The central vein in the hepatic lobule is always dilated, and the associated sinusoids are always engorged. In severe cases hemorrhage may also be seen in the sinusoids.

**Table 16.1** Hepatocyte toxicity of cytokines (Kupffer cell response to sepsis)

TNF- $\alpha$	Pro-inflammatory response and stimulation of IL-6 production by hepatocytes
IL-6	Pro-inflammatory response, stimulation of acute-phase proteins, and activation and release of TGF- $\beta$
IL-1 $\beta$	Pro-inflammatory response and synergistic action with TNF- $\alpha$
TGF- $\beta$	Anti-inflammatory response and counteracting of the extension of inflammatory response
IL-18	LPS-induced liver toxicity and secretion of IFN- $\gamma$
IFN- $\gamma$	HC apoptosis, elevation of TNF- $\alpha$ , and upregulation of CD14
IL-10	Anti-inflammatory response and downregulation of LPS-induced IL-6 release
	TNF tumor necrosis factor; IL interleukin; TGF transforming growth factor

After Nessler et al. [35]



Most patients have elevated jugular venous pressure, edema and occasionally an enlarged pulsatile liver due to tricuspid regurgitation. 25% of patients also have ascites. However, splenomegaly and an elevated hepatic venous portal gradient (HVPg) are classically absent in patients with heart failure and cardiac cirrhosis.

Sherlock et al. found greater liver damage in patients with longer duration of heart failure [46]. 12 out of 17 patients with grade C damage had heart failure for 60 days or more, compared to 5 out of 18 patients with Grade A damage.

One would intuitively expect a relationship between the right atrial pressure (signifying venous pressure and therefore propensity for passive venous congestion) and the extent of hepatic necrosis. Sherlock et al. found that 11/12 patients with severe hepatocyte necrosis had cardiac output less than 3.8 lit/min, however many patients with minimal cell necrosis also had conspicuously low cardiac outputs. Further, they did not find a significant correlation between the RA pressure and level of liver necrosis. Conversely, they found that the depth of jaundice correlated with the RA pressure. Bilirubin levels were higher in Grade B and C necrosis compared to Grade A. Patients with a higher RA pressure had a higher bilirubin level, but there was no correlation between serum bilirubin levels and cardiac output. The cause of jaundice in passive congestion due to heart failure was also unclear. Although the extent of liver cell necrosis correlates with the degree of jaundice, it is unlikely to be a complete explanation. Normal biliary secretory pressure approximate 20–30 cm water pressure. Therefore if the RA pressure exceeds 20 cm water, it can lead to mechanical obstruction of the intralobular biliary canaliculi. Formation of “bile thrombi” may also cause biliary obstruction. However, Sherlock et al. found that alkaline phosphatase was normal in most patients, making obstructive jaundice less likely to be the dominant factor in cardiac jaundice.

Lau et al. evaluated 110 charts for the type of liver dysfunction found in patients admitted to cardiology service for congestive heart failure (left or right) [47]. They excluded patients with evidence of acute myocardial infarction, and hemodynamic instability. All patients had NYHA Class II to IV heart failure. Elevation of GGT and reduction in albumin level were the most common abnormalities (41% each), followed by elevation in ALP (22%) and Bilirubin (19%). This suggested that a cholestatic pattern of LFTs (ALP, GGT and Bilirubin) was significantly more common than a hepatocellular pattern in patients with Class II to IV heart failure. Also, each of the cholestatic LFT elevations was significantly associated with the severity of tricuspid regurgitation (TR). The severity of TR, Pulmonary hypertension and left ventricular dysfunction were also independently associated with rise in bilirubin. Conversely none of these cardiac factors were associated with elevation of transaminases or hypoalbuminemia. Lau et al. surmised that backward con-

gestion of hepatic venules and pulsatile injury from TR have a greater role than reduced forward cardiac flow in causing liver dysfunction in heart failure.

Allen et al. evaluated data from the CHARM trial [48], and found that low albumin was the most common liver abnormality in patients with chronic systolic heart failure (18.2%), followed by elevation of total bilirubin (13%). ALT was elevated in only 3% of patients. Total bilirubin was strongest LFT predictor of adverse outcomes for composite of cardiovascular death or heart failure hospitalization.

Van Deursen et al. performed a retrospective chart review of 323 heart failure patients [49]. They found direct bilirubin and LDH to be the predominant LFT abnormality. Elevated CVP was significantly associated with abnormalities in all LFTs (GGT, ALP, Total Bilirubin, Direct Bilirubin, AST, ALT, and LDH). However, a low cardiac index (CI) was significantly associated with AST, ALT and total bilirubin only. Highest abnormalities were observed when both high CVP and low CI were present. Also, most LFTs showed an increase in percentages of abnormal values with increasing CVP and reducing CI. Importantly, in a univariate analysis, GGT, ALP, AST and LDH were predictors of all-cause mortality. However, after adjustment for CVP and CI, none of the LFTs were associated with impaired survival.

### 16.5.2 Ischemic Hepatitis

Low cardiac output may be associated with marked elevations in serum aminotransferases, caused by hepatocellular necrosis. This has been called “Ischemic hepatitis” “Hypoxic hepatitis” or “Shock Liver”. The eventual reason for hepatocellular necrosis is inadequate oxygen supply to hepatocytes, secondary to septic shock, cardiogenic shock, or hypoxemia due to respiratory failure. Therefore the term “hypoxic hepatitis” introduced by Henrion et al. might be the most appropriate.

Ischemic/hypoxic liver injury leads to necrosis of centrilobular (zone 3) hepatocytes since these are the farthest away from the portal triad (the oxygen source). Hepatocytes can increase oxygen extraction up to 95%. However, if hypoxic conditions persist, or the shock is severe, the protective mechanisms are overwhelmed and hepatocyte necrosis occurs. This leads to a rapid elevation in alanine aminotransferase (ALT) aspartate aminotransferase (AST) lactate dehydrogenase (LDH), bilirubin and prolongation of prothrombin time (PT). Laboratory changes peak in 1–3 days after the insult, and improve rapidly to normalize within 5–10 days.

Henrion et al. evaluated the liver dysfunction and hemodynamic abnormalities in 142 patients with a reason to have “hypoxic hepatitis” [50]. They included patient with decompensated congestive heart failure, acute cardiac failure, exacerbated hypoxic respiratory failure and toxic/septic shock. Hepatic blood flow was reduced in decompensated heart

failure without hypoxic hepatitis, and was significantly more reduced if hypoxic hepatitis was present. CVP was significantly more elevated in patients with decompensated CHF when hypoxic hepatitis was present. They postulated that the liver of patients with CHF is chronically exposed to hypoxia due to venous congestion, and the hypoxia is suddenly worsened during an episode of exacerbation leading to liver cell necrosis. The liver in patients with acute cardiac failure was not in an underlying hypoxic state, and therefore needed a more severe fall in hepatic blood flow during the acute event to undergo hypoxic hepatitis. Acute cardiac failure and circulatory failure groups had a higher percentage of patients in shock (SBP < 90 mmHg) as compared to the decompensated CHF group. These two groups also had higher lactate and creatinine levels than decompensated CHF group.

With hypoxic/ischemic hepatitis, AST, ALT and LDH showed striking elevations and rapid resolution in 7–14 days. AST peak was generally higher than ALT peak. Peak AST was significantly higher in the circulatory failure group compared to decompensated CHF group. Other transaminase levels were not significantly different between the decompensated CHF and acute cardiac failure group. Another biochemical hallmark of hypoxic hepatitis was a rapid drop in prothrombin level, with a nadir level observed as early as day 1, and complete recovery in about 1 week.

### 16.5.3 Summary of the Liver in Cardiac Dysfunction

CHF leading to elevated CVP, causing passive venous congestion of liver. This is manifested by a persistent increase in the biochemical markers of cholestatic liver disease, like GGT, Bilirubin and ALP. The reason may be an impairment of function and engorgement of the biliary canaliculi secondary to central vein engorgement due to elevated CVP. Severity of elevation of CVP and TR are correlated to the elevation in LFT abnormalities. However, after controlling for CVP and Cardiac index, none of the liver abnormalities are associated with a worse prognosis. Thus prognosis is still governed by the extent of the cardiac problem and liver abnormalities are a manifestation of the severity of the cardiac disease.

Hypoxic/ischemic hepatitis presents with a triad of dramatic rise in transaminases, fall in prothrombin activity, and alteration in renal function, in the clinical setting of hypoperfusion/shock. Hypotension (SBP < 90 mmHg), is not a prerequisite for development of hypoxic hepatitis.

#### Conclusion

Liver injury results as a consequence of multiple factors: the precipitating event for critical illness, the stress of hypoxemia and hypoperfusion related in part to cytokine generation from Kupffer cells and hepatocyte synthetic

focus as well as support measures including drug-induced liver injury and inadequate hemodynamic support with unremitting hypotension or volume overload. Clearly, critically ill patients with and without liver injury fare differently. Pre-morbid liver dysfunction even if sub-clinical or occult is associated with worse outcome. Earlier recognition to allow targeted implementation of strategies that may benefit is the immediate goal.

## References

1. Pant C, Olyae M, Gilroy R, Pandya PK, Olson JC, Oropeza-Vail M, Rai T, Deshpande A. Emergency department visits related to cirrhosis: a retrospective study of the nationwide emergency department sample 2006 to 2011. *Medicine*. 2015;94(1):e308.
2. Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, Kamath PS. Intensive care of the patient with cirrhosis. *Hepatology*. 2011;54(5):1864–72.
3. Kramer L, Jordan B, Druml W, Bauer P, Metnitz PG. Austrian Epidemiologic Study on Intensive Care, ASDI Study Group. Incidence and prognosis of early hepatic dysfunction in critically ill patients—a prospective multicenter study. *Crit Care Med*. 2007;35(4):1099–104.
4. Maynard ND, Bihari DJ, Dalton RN, Beale R, Smithies MN, Mason RC. Liver function and splanchnic ischemia in critically ill patients. *Chest*. 1997;111(1):180–7.
5. Koch A, Horn A, Duckers H, Yagmur E, Sanson E, Bruensing J, Buendgens L, Voigt S, Trautwein C, Tacke F. Increased liver stiffness denotes hepatic dysfunction and mortality risk in critically ill non-cirrhotic patients at a medical ICU. *Crit Care*. 2011;15(6):R266.
6. Ozawa K, Aoyama H, Yasuda K, et al. Metabolic abnormalities associated with postoperative organ failure. A redox theory. *Arch Surg*. 1983;118:1245–51.
7. Rolla G, Brussino L, Colagrande P, Dutto L, Polizzi S, Scappaticci E, Bergerone S, Morello M, Marzano A, Martinasso G, Salizzoni M, Bucca C. Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. *Hepatology*. 1997;26(4):842–7.
8. Cremona G, Higenbottam TW, Mayoral V, Alexander G, Demoncheaux E, Borland C, Roe P, Jones GJ. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J*. 1995;8(11):1883–5.
9. Fernandez Del Rio R, O'Hara ME, Holt A, Pemberton P, Shah T, Whitehouse T, Mayhew CA. Volatile biomarkers in breath associated with liver cirrhosis – comparisons of pre- and post-liver transplant breath samples. *EBioMedicine*. 2015;2(9):1243–50.
10. Kortgen A, Paxian M, Werth M, Recknagel P, Rauffuss F, Lupp A, Krenn CG, Muller D, Claus RA, Reinhart K, Settmacher U, Bauer M. Prospective assessment of hepatic function and mechanisms of dysfunction in the critically ill. *Shock*. 2009;32(4):358–65.
11. Cieslak KP, Huisman F, Bais T, Bennink RJ, van Lienden KP, Verheij J, Besselink MG, Busch ORC, van Gulik TM. Future remnant liver function as predictive factor for the hypertrophy response after portal vein embolization. *Surgery*. 2017;162(1):37–47.
12. Karvellas CJ, Pink F, McPhail M, Austin M, Auzinger G, Bernal W, Sizer E, Kutsogiannis DJ, Eltringham I, Wendon JA. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute on chronic liver failure. *Crit Care Med*. 2010;38(1):121–6.
13. Karvellas CJ, Bagshaw SM. Advances in management and prognostication in critically ill cirrhotic patients. *Curr Opin Crit Care*. 2014;20(2):210–7.

14. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastro*. 2013;144:1426–37.
15. Boone MD, Celi LA, Ho BG, Pencina M, Curry MP, Lior Y, Talmor D, Novack V. Model for End-Stage Liver Disease score predicts mortality in critically ill cirrhotic patients. *J Crit Care* 2014; 29(5):881.e7–13.
16. Schlichtig R, Klions HA, Kramer DJ, Nemoto EM. Hepatic dys-oxygenia commences during O<sub>2</sub> supply dependence. *J Appl Physiol*. 1992;72(4):1499–505.
17. Weemhoff JL, Woolbright BL, Jenkins RE, McGill MR, Sharpe MR, Olson JC, Antoine DJ, Curry SC, Jaeschke H. Plasma biomarkers to study mechanisms of liver injury in patients with hypoxic hepatitis. *Liver Int*. 2017;37(3):377–84.
18. Fuhrmann V, Jäger B, Zubkova A, Drolz A. Hypoxic hepatitis—epidemiology, pathophysiology and clinical management. *Wien Klin Wochenschr*. 2010;122:129–39.
19. Matuschak GM, Pinsky MR, Klein EC, Van Thiel DH, Rinaldo JE. Effects of D-galactosamine-induced acute liver injury on mortality and pulmonary responses to *Escherichia coli* lipopolysaccharide. Modulation by arachidonic acid metabolites. *Am Rev Respir Dis*. 1990;141(5 Pt 1):1296–306.
20. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303–10.
21. Brun-Buisson C, Meshaka P, Pinton P, Vallet B. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*. 2004;30:580–8.
22. Vincent JL, Angus DC, Artigas A, Kalil A, Basson BR, Jamal HH, Johnson G, Bernard GR. For the recombinant human activated protein C worldwide evaluation in severe sepsis (PROWESS) study group: effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med*. 2003;31:834–40.
23. Whitehead MW, Hainsworth I, Kingham JG. The causes of obvious jaundice in South West Wales: perceptions versus reality. *Gut*. 2001;48(3):409–13.
24. Chand N, Sanyal AJ. Sepsis-induced cholestasis. *Hepatology*. 2007;45(1):230–41.
25. Bhogal HK, Sanyal AJ. The molecular pathogenesis of cholestasis in sepsis. *Front Biosci*. 2013;5:87–96.
26. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):801–10.
27. Yan J, Li S, Li S. The role of the liver in sepsis. *Int Rev Immunol*. 2014;33(6):498–510.
28. Kobashi H, Toshimori J, Yamamoto K. Sepsis-associated liver injury: incidence, classification and the clinical significance. *Hepatol Res*. 2013;43(3):255–66.
29. Srivastava B, Gimson A. Hepatic changes in systemic infection. *Best Pract Res Clin Gastroenterol*. 2013;27(4):485–95.
30. Wang D, Yin Y, Yao Y. Advances in sepsis-associated liver dysfunction. *Burns Trauma*. 2014;2(3):97–105.
31. Howell MD, Davis AM. Management of sepsis and septic shock. *JAMA*. 2017;317(8):847–8.
32. Long CL, Maull KI, Krishnan RS, Laws HL, Geiger JW, Borghesi L, et al. Ascorbic acid dynamics in the seriously ill and injured. *J Surg Res*. 2003;109(2):144–8.
33. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151(6):1229–38.
34. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal*. 2013;19(17):2068–83.
35. Nessler N, Launey Y, Aninat C, Morel F, Malledant Y, Seguin P. Clinical review: the liver in sepsis. *Crit Care*. 2012;16(5):235.
36. Moreno R, Sprung CL, Annane D, Chevret S, Briegel J, Keh D, Singer M, Weiss YG, Payen D, Cuthbertson BH, Vincent J. Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the CORTICUS study. *Intensive Care Med*. 2011;37:1765–72.
37. Kubitz R, Wettstein M, Warskulat U, Häussinger D. Regulation of the multidrug resistance protein 2 in the rat liver by lipopolysaccharide and dexamethasone. *Gastroenterology*. 1999;116:401–10.
38. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology*. 2002;36:395–402.
39. Tsai MH, Peng YS, Chen YC, Liu NJ, Ho YP, Fang JT, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology*. 2006;43:673–81.
40. Marik PE. Tight glycemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med*. 2016;42(9):1475–7.
41. Mesotten D, Wauters J, Van den Berghe G, Wouters PJ, Milants I, Wilmer A. The effect of strict blood glucose control on biliary sludge and cholestasis in critically ill patients. *J Clin Endocrinol Metab*. 2009;94:2345–52.
42. Portella AO, Montero EF, deFigueiredo P. Effects of N-acetylcysteine in hepatic ischemia-reperfusion injury during hemorrhagic shock. *Transplant Proc*. 2004;39:846–8.
43. Farrell SJ, Aldag E, Pedersen R, Sahajpal A, Clendenon J, Gunabushanam V, Kramer DJ. Evaluation of the effects of N-Acetylcysteine treatment in adult liver transplant recipients. *J Pharm Soc Wis*. 2016;19(6):49–52.
44. Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. On behalf of the RELIEF study group. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology*. 2013;57:1153–62.
45. Dunn GD, Hayes P, Breen KJ, Schenker S. The liver in congestive heart failure: a review. *Am J Med Sci*. 1973;265(3):174–89.
46. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *Br Heart J*. 1951;13(3):273–93.
47. Lau GT, Tan HC, Krithrades L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol*. 2002;90:1405–9.
48. Allen LA, Felker GM, Pocock S, et al. CHARM investigators. Liver function abnormalities and outcome in patients with chronic heart failure: data from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Eur J Heart Fail*. 2009;11(2):170–7.
49. Van Deursen VM, Damman K, Hillege HL, et al. Abnormal liver function in relation to hemodynamic profile in heart failure patients. *J Card Fail*. 2010;16:84–90.
50. Henrion J, Schapira M, Luwaert R, et al. Hypoxic hepatitis. *Medicine*. 2003;82(6):392–406.

William J. Peppard, Alley J. Killian, and Annie N. Biesboer

### Abstract

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) have profound effects on human physiology that extend well beyond hepatic considerations. Virtually every organ system is affected to some degree, as are the medications used to treat both chronic and acute conditions for these organ systems. Even a small therapeutic misadventure can precipitate an acute decompensation in liver failure patients, further emphasizing the importance of appropriate drug dosing. Liver disease results in significant alteration in the pharmacokinetic and pharmacodynamic characteristics of medications. While the magnitude of these alterations is dependent upon the extent of liver disease and the physiochemical characteristics of a given medication, the effect of most medications will be amplified as a result of liver disease. This chapter provides a practical overview of drug dosing considerations, with a focus on basic pharmacokinetic and pharmacodynamics principles, in the context of ALF and ACLF. This is followed by medication considerations organized by organ system, with a focus on neurology, pulmonary, cardiovascular, renal, hematologic, gastrointestinal, and endocrine. Infectious disease considerations are also reviewed. The use of objective monitoring tools and the establishment of therapeutic goals will help facilitate the optimal use of drug therapy for each organ system. In many cases, treatment guidelines are lacking for the management of acute and chronic disease observed concurrently in patients with liver failure. Avoiding medications that have unpredictable pharmacokinetic profiles, or that are prone to drug-drug interactions, will reduce sequela. Employing evidence-based pharmacotherapy should yield improved outcomes. Practical considerations for the aforementioned are provided.

### Keywords

Liver failure • Cirrhosis • Pharmacokinetic • Pharmacodynamic • Metabolism • Drug dosing • Analgesia • Pain • Sedation • Agitation • Antiepileptic • Synthetic prostacyclin • Phosphodiesterase inhibitor • Endothelin receptor antagonists • Vasopressor • Beta-blocker • Antiarrhythmic • Hepatorenal syndrome • HRS • Stress ulcer prophylaxis • Proton pump inhibitor • Histamine-2 receptor antagonists • Anti-emetic • Venous thromboembolism

W.J. Peppard, PharmD, BCPS, FCCM (✉)  
A.N. Biesboer, PharmD, BCPS, BCCCP  
Medical Critical Care, Department of Pharmacy, Froedtert & the  
Medical College of Wisconsin, Milwaukee, WI, USA  
e-mail: [william.peppard@froedtert.com](mailto:william.peppard@froedtert.com);  
[annie.biesboer@froedtert.com](mailto:annie.biesboer@froedtert.com)

A.J. Killian, PharmD, BCPS  
Surgical Critical Care, Department of Pharmaceutical Services,  
Emory University Hospital, Atlanta, GA, USA  
e-mail: [alley.killian@emoryhealthcare.org](mailto:alley.killian@emoryhealthcare.org)



prophylaxis • VTE • Anticoagulation • Heparin-induced thrombocytopenia • HIT  
 Infectious disease • Antibiotic • Glycemic control • Thyroid • Relative adrenal insufficiency  
 RAI • Steroid • Continuous renal replacement therapy • CRRT • Extracorporeal liver  
 support • ECLS • Extracorporeal membrane oxygenation • ECMO

## Learning Objectives

- Describe the basic pharmacokinetic and pharmacodynamic alterations that occur in patients with liver disease.
- Identify key medications that require dosing adjustments in patients with liver failure.
- Given a patient case with liver disease, select the most appropriate therapeutic recommendation.
- Discuss the effect of extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT) and extracorporeal liver support systems on medications in patients with liver failure.

## 17.1 Pharmacokinetics/ Pharmacodynamics

Liver disease results in significant alteration in the pharmacokinetic and pharmacodynamic characteristics of medications. Unfortunately there are no endogenous markers of hepatic clearance, and the most common scoring tool used for characterizing liver disease, the Child-Pugh classification, does not correlate well with hepatic clearance or drug metabolism in liver disease. While the magnitude of these alterations is dependent upon the extent of liver disease and the physiochemical characteristics of a given medication, the effect of most medications will be amplified as a result of liver disease.

### 17.1.1 Absorption

Delayed gastric emptying in patients with liver dysfunction can result in delayed absorption; this is a minor determinant in the extent of absorption [1, 2]. More significant is the affect that changes in first-pass metabolism have on bioavailability. Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport system of the liver before reaching systemic circulation [3]. In patients with normal liver function, drugs with a moderate to high extraction ratio will undergo significant first-pass metabolism, which is a function of mesenteric blood flow passing through the liver. Liver dysfunction leads to porto-systemic shunting and subsequently decreased

activity of drug-metabolizing enzymes, resulting in a substantial increase in systemic bioavailability. This effect is further exacerbated in patients with a transjugular intrahepatic porto-systemic shunt (TIPS). Orally administered midazolam bioavailability can be increased tenfold in cirrhotic patients with TIPS compared to cirrhotic patients without [4]. This is largely the result of decreased intestinal cytochrome P450 (CYP) 3A activity [5]. It should be noted that first-pass metabolism is bypassed altogether when medications are administered intravenously and therefore should not affect bioavailability.

### 17.1.2 Distribution

The distribution of medications is predominantly altered by changes in volume and protein binding [3]. Patients with hepatic cirrhosis are often volume overloaded as a result of fluid retention and ascites. This results in an increased volume of distribution ( $V_d$ ) which has the greatest effect on hydrophilic (water soluble) medications. Beta-lactam drugs can have a  $V_d$  as much as threefold larger [6]. This necessitates an increased dose, and perhaps a loading dose, in order to achieve and maintain therapeutic serum concentrations. Circulating plasma proteins are also low in patients with liver disease, especially chronic disease. Highly protein bound drugs are most affected, resulting in greater circulating free drug in the serum. This is predominantly due to decreased binding to albumin and  $\alpha_1$ -acid glycoprotein as a result of decreased protein synthesis, qualitative changes in protein binding sites, and accumulation of endogenous compounds, such as bilirubin, that inhibit plasma protein binding [7]. This is particularly problematic for medications with narrow therapeutic range and necessitates increased monitoring.

### 17.1.3 Metabolism and Elimination

Most data about drug metabolism are derived from patients with stable chronic liver disease; studies in patients with ALF are largely underrepresented. In general the degree of drug metabolism and elimination impairment parallels the degree of liver disease, but more specifically it is determined by the intrinsic hepatic drug clearance, hepatic blood flow, and the extent of plasma protein binding of a given drug.

Intrinsic hepatic drug clearance represents the metabolism of unbound drug by the liver, though not all metabolic pathways are affected equally [3, 8]. Phase II conjugative metabolism is relatively less affected than phase I oxidative metabolism, which consists of the enzymes CYP and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent CYP reductase. In general these enzymes are more sensitive to changes in liver function because of their dependence on oxygen [9]. Further declines in liver blood flow as a result of disease progression or placement of a TIPS may compound these effects. The Model for End-Stage Liver Disease (MELD) score has been correlated with CYP activity.

Hepatic blood flow is another important determinant of drug metabolism by the liver, especially for drugs with a high extraction ratio. The hepatic extraction ratio of a drug, which can be categorized as low ( $<0.3$ ), intermediate ( $0.3$ – $0.6$ ), or high ( $>0.6$ ), indicates the efficiency with which the liver can eliminate a given compound from the circulation, and is determined by intrinsic drug clearance and protein binding. Drugs with high extraction ratio are highly dependent on liver blood flow and demonstrate increased bioavailability in low-flow states, but are less influenced by changes in the activity of drug metabolizing enzymes and protein binding. Conversely, the metabolism of drugs with low extraction ratio is much more sensitive to changes in hepatic enzyme function and protein binding and relatively less affected by decreased hepatic blood flow. Drugs with intermediate extraction ratio may have variable bioavailability but generally exhibit decreased clearance in the setting of reduced liver function.

The changes in protein binding associated with acute and chronic liver disease can have variable effects on drug metabolism because they can influence both  $V_d$  and extraction ratio of a drug. Highly protein-bound drugs in the setting of hypoalbuminemia will distribute more extensively into tissues, making less total drug available in the circulation. Increased

unbound fraction can lead to potentially increased clinical effects due to higher free drug concentrations, but can also increase hepatic clearance by presenting more unbound drug to the liver for metabolism. This would be especially true for drugs with low extraction ratio. The ultimate clinical effects are therefore difficult to predict, but generally speaking drugs with low protein binding and low intrinsic hepatic clearance are most likely to demonstrate reduced hepatic clearance in liver failure. In addition to decreased metabolism, extrahepatic drug elimination may also decrease as liver function declines. Cholestasis may result in reduced biliary excretion of certain medications. Additionally, the development of renal dysfunction, such as hepatorenal syndrome (HRS), is common in decompensated liver disease.

## 17.2 Neurology

Management of neurologic derangements is common and challenging in patients with liver disease, and may include the chronic management of psychiatric and seizure medications, and the acute management of analgesia, sedation, and delirium. The Society of Critical Care Medicine has provided evidence-based clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit (ICU) [10]. There are no specific recommendations made for patients with liver disease, however the guidelines are largely generalizable and it is reasonable to apply basic principles to this population. The practice of monitoring for safety and efficacy and establishing therapeutic goals is universal, whereas medication selection requires greater appreciation for disease- and patient-specific variables. When selecting drug therapy one must consider the altered pharmacokinetic profile imposed by end-stage liver disease (ESLD) and dose medications appropriately to avoid adverse events. Tables 17.1

**Table 17.1** Analgesia summary of recommendations

Medication	Place in therapy	Considerations
Acetaminophen	Preferred agent	<ul style="list-style-type: none"> <li>• Well tolerated in patients with liver disease including cirrhosis.</li> <li>• Limit daily dose to 2 g/day (up to 3 g/day for short-term use).</li> </ul>
Tramadol	Use sparingly with caution	<ul style="list-style-type: none"> <li>• Can precipitate or worsen hepatic encephalopathy, but potentially less than opioids, and may be preferred.</li> <li>• Dose reduction is required.</li> </ul>
Opioids	Use sparingly with caution	<ul style="list-style-type: none"> <li>• All opioids can precipitate or worsen hepatic encephalopathy.</li> <li>• Variable effect and response dependent on individual agent.</li> <li>• Fentanyl preferred (short-acting agents with minimal accumulation).</li> <li>• Hydromorphone is an alternative.</li> <li>• Dose reduction is required.</li> </ul>
NSAIDs	Avoid use	<ul style="list-style-type: none"> <li>• Bioavailability increased in patients with liver impairment.</li> <li>• Increased risk of gastrointestinal bleed, variceal hemorrhage, acute kidney injury, and development of diuretic-resistant ascites.</li> </ul>
Other	Patient-specific consideration	<ul style="list-style-type: none"> <li>• Anticonvulsants and antidepressants are generally avoided due to concern for altered mentation.</li> <li>• Nortriptyline and desipramine appear less sedating and are preferred if absolutely necessary.</li> </ul>

**Table 17.2** Sedative summary of recommendations

Medication	Place in therapy	Considerations
Lorazepam	Preferred agent for intermittent sedation	<ul style="list-style-type: none"> <li>• Metabolic pathway less affected by cirrhosis compared to other benzodiazepines.</li> <li>• No active metabolites.</li> </ul>
Propofol	Preferred agent for continuous sedation	<ul style="list-style-type: none"> <li>• Well tolerated in patients with cirrhosis.</li> <li>• Pharmacokinetic profile is minimally altered in liver failure.</li> <li>• Concern for hypotension and deep sedation.</li> </ul>
Dexmedetomidine	Relative contraindication - avoid use	<ul style="list-style-type: none"> <li>• Clearance significantly reduced by liver dysfunction.</li> <li>• Hypotension and bradycardia are common.</li> </ul>
Midazolam	Relative contraindication - avoid use	<ul style="list-style-type: none"> <li>• Clearance significantly reduced by liver dysfunction.</li> <li>• Renally-cleared active metabolite with an unpredictable half-life.</li> <li>• Concern for hypotension and deep sedation.</li> </ul>

and 17.2 provide recommendations for the management of pain and agitation. The most common, often preventable complications include hepatic encephalopathy, acute kidney injury, and gastrointestinal bleeding. Severity of these adverse effects range from mild to serious and can sometimes be fatal [11]. Guidelines for the management of psychiatric and seizure medications in the context of liver failure are not available, but the same basic principles apply when selecting drug therapy. Considerations for drug selection and monitoring will be discussed further.

## 17.2.1 Analgesics

### 17.2.1.1 Monitoring

Patients in the ICU, including those in liver failure, routinely experience pain [10]. The etiology is multifactorial and can include injuries incurred prior to admission, surgery, procedures, line placement, endotracheal tube placement, or other routine ICU cares. As such, pain should be routinely monitored in all patients using an objective and validated tool. The Numeric Pain Score (NPS) and the Visual Analogue Scale (VAS) are most reliable and should be used in patients who can assess and communicate their own pain [10]. For those patients with altered mentation, including encephalopathic patients, the Behavioral Pain Scale (BPS) or Critical-Care Pain Observation Tool (CPOT) is recommended [10]. Rather than using non-specific symptoms and physiologic signs such as vital signs, perspiration, or nausea and vomiting, these tools use more specific criteria such as facial expression, body movement, muscle tension, and vocalization or compliance with mechanical ventilation. Regular use of these validated tools can lead to optimal use of medications and better pain management, thereby facilitating improved clinical outcomes in critically ill patients [10, 12, 13].

### 17.2.1.2 Acetaminophen

Acetaminophen (APAP) is a known hepatotoxin and is the leading cause of drug-induced ALF, accounting for nearly 50% of all cases of ALF in the United States [14]. These findings may lead prescribers to avoid APAP use in patients with known liver disease [15]. Data suggests that short-term therapeutic doses of  $\leq 4$  g/day of APAP do not result in drug accumulation in patients with nonalcoholic cirrhosis, nor do they cause significant changes in liver function tests; rather, unintentional APAP intoxication over a long period of time is the most common cause of ALF [14, 16–18]. APAP can produce dose-related hepatocellular necrosis, particularly in the setting of chronic alcohol consumption, in which even prescribed doses of APAP are sufficient to produce acute hepatitis [19, 20]. Those with alcoholic cirrhosis are particularly vulnerable to APAP-induced hepatotoxicity as they experience an increase in N-acetyl p-benzoquinone imine (NAPQI, a hepatotoxic metabolite), production via enzymatic induction and decreased levels of glutathione which neutralizes NAPQI [16, 17, 21]. APAP use in patients with alcoholic cirrhosis should be used at the lowest effective dose, not to exceed 2 g/day (up to 3 g/day for short-term use), and chronic use should be avoided. For moderate to severe pain, the short-term use of appropriately-dosed APAP is preferred over other analgesics that are associated with more serious adverse effects, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [15].

### 17.2.1.3 Opioid

Opioids should be used cautiously in patients with chronic liver disease because they can precipitate or contribute to worsening hepatic encephalopathy [16, 17, 22–24]. In the setting of acute liver injury, opioids should be used even more sparingly. When opioid use is unavoidable, fentanyl is the preferred opioid as its pharmacokinetic profile, relative to other opioids, remains unchanged [22, 23]. Bearing in mind the

quick onset and short duration of action, therapy should be initiated at a reduced dose and given less frequently, then titrated to effect. Hydromorphone demonstrates increased bioavailability and a prolonged half-life but is a viable alternative to fentanyl at a reduced dose. Codeine requires metabolism via CYP to be converted to morphine. Reduced metabolism in patients with liver disease makes codeine ineffective as an analgesic. Morphine should be avoided in patients with liver disease; it is metabolized by the liver to an active metabolite which is heavily dependent upon renal function for clearance. This, along with increased bioavailability, results in a prolonged half-life and exaggerated pharmacologic effect fostering unpredictable kinetics and potentially unsafe use. Similarly, oxycodone demonstrates a prolonged half-life in liver disease and may accumulate. Meperidine exhibits similar pharmacokinetic changes, but accumulation of neurotoxic metabolites makes it an especially poor choice for pain management during liver disease. The clearance of methadone is reduced in ESLD, though it is free from active metabolites. Because of this, some advocate for its use in moderate liver failure despite its difficulty to use in healthy adults because of its highly variable and unpredictable pharmacokinetic profile. To date a consensus has not been reached on the role of methadone in liver disease. Opioid-dependent patients present a unique challenge in the context of acute, decompensated liver failure. Opioids should be prescribed sparingly in the context of encephalopathy but consideration must be paid to the risk of withdrawal. The lowest effective dose of opioid, preferably fentanyl, should be used and titrated to effect.

#### 17.2.1.4 Other

Several other medications have been evaluated in patients with liver disease as opioid alternatives for the management of acute and chronic pain, especially neuropathic pain. Tramadol, which has both a hepatic metabolic and renal elimination component, has been recommended as a treatment option before proceeding to opioids based on its favorable safety profile [11]. As with other medications, a dose reduction and increased monitoring is warranted. Other medications such as anticonvulsants (carbamazepine, gabapentin, pregabalin) and tricyclic antidepressants (TCA) are common for chronic pain management, but are generally avoided in liver failure given concern for altered mentation. However, if a TCA is deemed necessary, nortriptyline and desipramine appear less sedating and are preferred.

#### 17.2.1.5 NSAIDs

The risk of NSAID use in the setting of liver dysfunction is often underestimated. Health care professionals frequently endorse the use of NSAIDs in this population while recommending the avoidance of APAP use in patients with liver disease or cirrhosis [15]. Although occurrences are rare,

these agents can independently produce idiosyncratic acute hepatocellular necrosis or cholestatic damage, which could precipitate an episode of ACLF [19, 25, 26]. More concerning is their deleterious effect on renal function. Mediated by prostaglandin (PG) synthesis inhibition, NSAIDs impair their protective renal vasodilating effect. Though not generally a concern in normotensive adults, inhibition of PG synthesis leads to renal decompensation in scenarios such as cirrhosis where renal and systemic hemodynamics are dependent on the availability of PGs [27]. This may result in blunting of the natriuretic effect of diuretics, as well as decreased sodium and water excretion, creatinine clearance, and glomerular filtration rate, both in patients with compensated disease and decompensated cirrhosis [28–34]. NSAIDs have also been associated with variceal bleeding in patients with liver failure [35]. In summary, these adverse effects are generally considered a class effect and NSAIDs should be avoided in patients with hepatic cirrhosis.

### 17.2.2 Sedatives

Critically ill patients are frequently anxious and agitated due to procedures and invasive therapies, such as mechanical ventilation and invasive lines. Sedatives reduce agitation and anxiety, thereby keeping patients more comfortable and safe during their ICU encounter [10]. There are several therapeutic options available to prescribers to establish and maintain safe and effective sedation, but selection of therapy must be patient-specific, taking into consideration how acute and chronic diseases will affect the pharmacokinetic profile of the drug.

#### 17.2.2.1 Therapeutic Goals

Depth of sedation should be routinely monitored in all patients using an objective and validated tool. The Sedation Agitation Scale (SAS) and the Richmond Agitation Sedation Scale (RASS) are validated in critically ill patients, though not specifically in patients with liver disease [10]. Light sedation (SAS 3–4 or RASS 0 to –1) is preferred to deep sedation as it has been associated with decreased duration of mechanical ventilation and lower mortality. Once sedation goals are established, the least amount of sedative necessary to maintain patient comfort and safety should be used.

#### 17.2.2.2 Propofol

Propofol is an intravenous general anesthetic that exerts its effect through agonism of gamma-Aminobutyric acid (GABA) receptors and perhaps reduced glutamatergic activity through N-Methyl-D-aspartic acid (NMDA) receptor blockade. It is a short-acting medication that is cleared rapidly and linear pharmacokinetics have been observed with infusion in healthy patients [36–38]. Its pharmacokinetic



profile does not appear to significantly change in patients with moderate hepatic cirrhosis, defined as those without ascites or encephalopathy [37]. Although the recovery time was longer in patients with cirrhosis and  $V_d$  at steady state was larger, total body clearance and terminal elimination half-life were unchanged. While the drug undergoes extensive hepatic metabolism, additional extra-hepatic metabolism prevents significant drug accumulation in patients with cirrhosis. Short-term propofol use during endoscopic procedures in patients with liver failure has demonstrated an incidence of adverse effects similar to other sedative agents and does not precipitate hepatic encephalopathy, but post anesthetic recovery following procedural sedation may be delayed compared to healthy subjects [39–42]. Cessation of propofol infusion results in a more rapid return to baseline function compared to midazolam [43–46]. Common but serious side effects include respiratory depression, hypotension (attributed to systemic vasodilation which is more pronounced in hypovolemic patients), hypertriglyceridemia, and cardiac dysrhythmias. Hypotension, which can also lower intracranial pressure, may theoretically worsen hepatic encephalopathy, is generally proportional to dose and rate of administration. Propofol infusion syndrome (PRIS) is defined as metabolic acidosis and cardiac dysfunction, along with one of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure [47]. PRIS is a rare but life-threatening complication with mortality rates ranging from 18 to 83% [48, 49]. Liver disease has not been identified as a risk factor for PRIS, but rate and duration of infusion are strong predictors. For this reason it is recommended that infusions greater than 65 mcg/kg/min for longer than 48 h be avoided [49]. Propofol should immediately be discontinued if PRIS is suspected, although complications and even death may ensue after propofol discontinuation, because there is no known antidote. All things considered, propofol appears to be safe and effective in liver failure and is the preferred agent for sedation due to its short half-life, fast onset, and decreased recovery time compared to other agents [50–53].

#### 17.2.2.3 Dexmedetomidine

Dexmedetomidine is a centrally-acting alpha-2 receptor agonist that is routinely used in the ICU to provide light sedation for patients requiring mechanical ventilation. Data suggests that dexmedetomidine is a safe and effective alternative to a midazolam infusion and may yield a shorter duration of mechanical ventilation and ICU length of stay, and potentially lower incidence of delirium, which together can significantly lower total ICU costs in critically ill patients [54–57]. Dexmedetomidine is extensively metabolized in the liver by CYP and glucuronidation to inactive metabolites. Since it is a high-extraction ratio drug, changes in hepatic blood flow can significantly affect clearance. Dexmedetomidine use in liver dysfunction, marked by increased aspartate aminotransferase

(AST) and bilirubin, is associated with delayed clearance and prolonged half-life, which may lead to significant delays in emergence from sedation, and an exaggerated side-effect profile [58–60]. Reduction in sympathetic tone caused by dexmedetomidine may be particularly problematic in patients with vasoplegia caused by hepatic failure, as the compensatory mechanisms are impaired, resulting in profound bradycardia and hypotension. Given these risks, dexmedetomidine should be judiciously dosed and monitored if used in patients with liver dysfunction, or avoided all together.

#### 17.2.2.4 Benzodiazepine

Prior to the introduction of newer sedative agents like propofol and dexmedetomidine, benzodiazepines were the mainstay of sedative therapy for critically ill patients [10, 61]. Lorazepam and midazolam have been the most commonly prescribed benzodiazepines for this purpose, where midazolam has traditionally been used for short-term sedation and lorazepam for long-term sedation. However, all benzodiazepines are metabolized by the liver. This results in reduced metabolism and prolonged elimination in patients with liver dysfunction, especially when compared to propofol [43–46, 62–64]. These altered pharmacokinetic parameters are further augmented in elderly patients or those concurrently administered medications that inhibit CYP enzyme systems and/or glucuronide conjugation in the liver. Taken together, these characteristics can result in prolonged sedation and may precipitate or worsen hepatic encephalopathy [10, 65, 66]. Hepatorenal syndrome is a common complication in acutely ill hepatic cirrhosis patients. Given that midazolam has an active metabolite which is renally eliminated, the use of midazolam in patients with combined liver and kidney impairment can further prolong sedation and should be avoided [67–70]. Should a benzodiazepine be necessary, lorazepam is generally thought to be the drug of choice because its primary mechanism of metabolism, conjugation, is a process less affected by liver dysfunction [71–73]. When using lorazepam in patients with liver disease, the dose should be empirically reduced and given less frequently, thus utilizing the lowest effective dose to minimize undesirable adverse effects. Midazolam use should be avoided.

### 17.2.3 Antiepileptics

Antiepileptic drug (AED) therapy warrants detailed clinical assessment in the setting of liver failure because some of these agents (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, valproate, etc.) are known to cause liver failure. Even if not the cause of liver failure, most AEDs are hepatically metabolized to some extent and necessitate dose adjustments in the setting of liver failure [74–76]. The ability to balance the effects of these agents on the liver while continu-

ing to ensure safe and effective seizure control can be challenging. During the initial workup and management of ALF all medications, especially AEDs, should be screened as a potential etiology [77]. Any drug thought to be associated with causing ALF should be immediately discontinued and alternative therapy considered. Consideration for alternative therapy should primarily include AED outcome data for the patient's specific seizure type. In addition, one must also consider mechanism of action, drug interactions, and side effect profile with particular attention paid to the potential of worsening hepatic encephalopathy [78]. However, this can be difficult given that most AEDs are hepatically metabolized to some extent [74–76].

Phenytoin, levetiracetam, and more recently lacosamide, are three AEDs commonly used in contemporary practice. Phenytoin has a narrow therapeutic window and demonstrates non-linear kinetics in healthy adults; this is further amplified in patients with liver disease due to its high protein binding, low extraction ratio, and CYP2C9 and CYP2C19 metabolic pathways [74, 75, 79]. Lower doses should be used during liver failure and therapeutic drug monitoring of free phenytoin levels should be employed. Phenytoin also has many significant drug-drug interactions which further complicate its roles in therapy. In general, newer agents yield similar efficacy to older agents but have a more favorable adverse drug reaction profile and fewer drug-drug interactions. Levetiracetam exhibits low protein binding and a low extraction ratio with approximately 24% metabolized via hydrolysis; the remainder is excreted unchanged by the kidneys. Dose adjustments are not necessary in liver dysfunction, but drug accumulation has been observed in renal failure and warrants dose reduction. Few drug-drug interactions and a favorable adverse effect profile make levetiracetam a first-line agent. Similar to levetiracetam, lacosamide exhibits low protein binding and a low extraction ratio, but is slightly more dependent upon the liver for metabolism through the CYP2C9, CYP2C19, and CYP3A4 pathways [74, 75, 79]. Drug accumulation does occur as liver function decreases so empiric dose reductions are recommended.

## 17.3 Cardiovascular

Cirrhosis is a hyperdynamic state and patients frequently exhibit low systemic vascular resistance, increased cardiac output and heart rate, and low mean arterial pressure (MAP) at baseline. The constellation of findings indicative of the structural abnormalities as well as functional changes that can be found in cirrhotic patients have been termed cirrhotic cardiomyopathy. These changes include the previously mentioned alterations in hemodynamic parameters as well as systolic and diastolic dysfunction and electrophysiological changes. The presence of cirrhotic cardiomyopathy can have

a significant effect on how patients respond in periods of increased stress such as critical illness, surgery, and infection and can make management of hemodynamics in the critical care setting challenging as the hemodynamic manifestations are often enhanced. Extensive discussion regarding cardiovascular pathophysiology in liver disease is discussed in detail elsewhere in this textbook. Many of the parenteral cardiovascular medications used in the ICU setting have a fast onset, short duration, and readily measurable effects and can be dosed to a clinical goal such as blood pressure. This makes it easier to determine if liver disease is affecting the response to these medications and if dosing modifications are indicated.

### 17.3.1 Vasopressors

Vasopressors are frequently required to maintain adequate perfusion in critically ill patients with both ALF and ACLF. Shock can be the result of a variety of insults including, but not limited to, decompensated liver failure resulting in a vasodilatory state, septic shock, and hemorrhagic shock. Norepinephrine is considered the vasopressor of choice for distributive shock in patients with cirrhosis as its stimulation of both alpha and beta-receptors increases MAP due to vasoconstrictive effects while preserving cardiac output with little increase in stroke volume compared with dopamine. There are no dosing recommendations specific to patients with liver disease and vasopressors can be titrated to patient-specific hemodynamic goals. Dopamine should generally be avoided because it could cause vasodilation of the splanchnic circulation thereby worsening portal hypertension [80].

Vasopressin has been used as an adjunct to catecholamines for the treatment of shock and has been found to be catecholamine-sparing in the setting of septic shock [81]. Vasopressin may be of particular benefit in patients who also have HRS as it has been shown to improve outcomes related to that disease state [82].

### 17.3.2 Beta-adrenoreceptor Antagonists and Calcium Channel Blockers

Beta-adrenoreceptor antagonists (more commonly referred to as beta blockers or  $\beta$ -blockers) are used in the critical care setting for a variety of indications including hypertension, tachycardia, and arrhythmias. Metoprolol is a commonly used selective  $\beta$ -blocker which is metabolized by the liver via several different metabolic pathways [83]. It is a high extraction ratio medication so bioavailability is increased in liver disease (from 50% in normal subjects to 80% in cirrhosis). In addition, the area under the curve (AUC) was markedly increased and the elimination half-life was prolonged follow-

ing both oral and intravenous doses [84]. Dose reduction by a factor of two to three has been recommended [83]. Labetalol, a nonselective  $\beta$ -blocker commonly used in the ICU setting, is also hepatically metabolized and has a high extraction ratio [2]. Therefore, similar consideration should be given to a possible prolonged half-life and need for dose reduction.

### 17.3.3 Calcium Channel Blockers

Nicardipine is a calcium channel blocker which is primarily used in its parenteral form as a continuous infusion for hypertensive emergency or urgency in the critical care setting. It undergoes extensive hepatic metabolism and has a high extraction ratio [2]. The pharmacokinetics of nicardipine can be described as a three-compartment model. The alpha and beta half-lives are both short at under one hour, however the terminal half-life is over 12 h which is seen with long-term infusions. Due to its hepatic metabolism, this is even longer in patients with liver disease. Although, titration to specific clinical goals is appropriate, titration should occur slowly with close hemodynamic monitoring and dose reduction may be necessary in patients with liver disease.

### 17.3.4 Antiarrhythmics

The majority of antiarrhythmics are metabolized by the liver and have a narrow therapeutic index making dose adjustments clinically significant in this patient population. This section will focus on the more commonly used antiarrhythmics in the non-cardiac critical care setting such as those used for atrial fibrillation. Amiodarone is likely the most commonly used antiarrhythmic in non-cardiac ICUs and is available as both oral and parenteral formulations. It is extensively metabolized by the liver and has a very long half-life in patients without liver disease after prolonged oral administration (25–53 days) [85, 86]. Although there are no data specific to amiodarone in liver disease, it can be assumed that metabolism would be impacted resulting in an even longer half-life [83]. Diltiazem, a class IV antiarrhythmic used for rate control in atrial fibrillation, is available in an oral form but is usually used in the ICU in its parenteral form as a continuous infusion. It is extensively metabolized by the liver resulting in decreased clearance in patients with liver dysfunction. A small study of long-term oral administration in cirrhosis demonstrated a slightly prolonged half-life and increased AUC of diltiazem and one of its active metabolites [87]. An empiric dose reduction by a factor of two has been suggested [83].

An additional cardiovascular consideration in patients with cirrhosis is QT interval prolongation which is frequently associated with cirrhotic cardiomyopathy and can worsen as severity of cirrhosis worsens. The prevalence of QT prolon-

gation has been reported to be as high as 60% in patients with Child-Pugh grade C cirrhosis [88]. Therefore, evaluation of the baseline QT interval and continued monitoring is vital as is assessment of medications with risk of QT prolongation.

## 17.4 Pulmonary

Pulmonary complications are common in ESLD [1, 2, 89]. Standard supportive care medication therapies for dyspnea and hypoxia (e.g. albuterol, inhaled steroids, etc.) can commonly be prescribed in this patient population without need for dosing adjustments. However, more severe complications, such as portopulmonary hypertension may require treatment with pulmonary vasodilatory therapies such as synthetic prostacyclins, phosphodiesterase inhibitors and endothelin receptor antagonists [21, 89–94]. These particular medications may require more thoughtful monitoring and dosing adjustments in the ESLD patient population as described below.

### 17.4.1 Synthetic Prostacyclins

Synthetic prostacyclins such as epoprostenol, treprostinil, and iloprost have established efficacy in the treatment of portopulmonary hypertension [89]. However, the pharmacokinetics of these agents, particularly clearance, may be significantly altered in patients with hepatic impairment.

The pharmacokinetics of intravenous iloprost was evaluated in eight hospitalized patients suffering from liver cirrhosis. Pharmacokinetic parameters were collected throughout the inpatient treatment course [95]. The study demonstrated that iloprost clearance was one-half in patients with hepatic impairment. The authors concluded that initial starting doses should be reduced by at least one-half the standard dose and patients should receive dose titrations based on individual parameters.

Epoprostenol has the shortest half-life amongst the synthetic prostacyclins, which is estimated to be approximately six minutes [96]. However, given the lack of available chemical assay to assess the *in vivo* pharmacokinetics of epoprostenol, no specific studies to date exist evaluating the impact of hepatic impairment on this medications pharmacokinetics.

To date, treprostinil has the most data specifically focused on use in hepatic impairment. According to its package insert, both intravenous and subcutaneous treprostinil is documented to have decreased clearance in patients with hepatic impairment [97]. It is recommended that for the treatment of pulmonary hypertension, that the initial dose be decreased to 0.625 ng/kg/min ideal body weight in patients with mild to

moderate hepatic impairment. However, there are no formalized studies to date that evaluate the use of intravenous or subcutaneous treprostinil in patients with severe hepatic impairment.

Most recently, oral treprostinil was approved by the United States Food and Drug Administration. The availability of an oral prostacyclin provides a simplified administration route of therapy for patients with pulmonary hypertension. However, there are limited data for the use of this particular synthetic prostacyclin in portopulmonary hypertension. Regardless, there is significant potential that this therapy will be used in the future for treatment of this unique subset of patients. Fortunately, this agent has the most robust data evaluating its pharmacokinetics in the liver disease patient population. Peterson and colleagues completed a small evaluation of the pharmacokinetics of oral treprostinil, treprostinil diolamine, in thirty subjects with various degrees of hepatic impairment [98]. With increasing severity of hepatic impairment, the mean treprostinil clearance decreased, resulting in increased levels of treprostinil. Adverse effects, such as headache, nausea, etc., were more commonly experienced in the patients with hepatic impairment. In clinical practice, oral treprostinil should be dose cautiously, and patients should be monitored closely for adverse effects.

Clinical interpretation of these data indicates the need to start synthetic prostacyclins, except epoprostenol, at lower doses in patients with hepatic impairment. Similarly, clinicians should cautiously titrate doses while monitoring closely for adverse effects. However, epoprostenol's uniquely short half-life makes it the likely exception to this rule and can likely be initiated and titrated regardless of hepatic function.

#### 17.4.2 Phosphodiesterase Inhibitors

There is increasing evidence supporting the use of sildenafil and tadalafil in patients with portopulmonary hypertension [89, 94].

Sildenafil undergoes metabolism via CYP3A4 and CYP2C9 to form an active metabolite [99]. It would be anticipated that this metabolism would be altered in a patient with hepatic impairment. Although the manufacturer of Revatio®, sildenafil marketed for pulmonary hypertension, provides no dose adjustment recommendations, the manufacturer for Viagra®, sildenafil marketed for erectile dysfunction, suggests a lower starting dose in patients with hepatic dysfunction [99, 100]. Therefore, it may be pertinent to be cautious with aggressive dosing of sildenafil, regardless of indication, in patients with hepatic impairment.

Similarly to sildenafil, tadalafil is primarily metabolized by CYP3A. According to the tadalafil package insert, initial pharmacokinetics studies have shown that mild to moderate hepatic impairment did not impact the amount of tadalafil

exposure the patient experiences [101]. However, in patients with Child Pugh Class A or B hepatic impairment, the manufacturer recommends to consider starting at a dose of 20 mg once per day or less. However, they state that due to lack of literature evaluating the use of tadalafil in patients with severe hepatic impairment, it should be avoided.

Apart from manufacturer recommendations, tadalafil pharmacokinetics in patients with hepatic impairment was evaluated by Forgue and colleagues [102]. This study evaluated tadalafil pharmacokinetics in a total of twenty-five patients with some degree of hepatic impairment. However, only one patient was classified as having severe impairment. Their evaluation found a trend towards lower tadalafil concentrations and prolongation in half-life with increasing severity of impairment; however, no statistical association was found.

Data regarding the use of both sildenafil and tadalafil in patients with hepatic impairment are limited and inconsistent. Error on the side of caution and starting at lower doses is likely most appropriate in most patients, but more aggressive dosing is not excluded by the data published to date.

#### 17.4.3 Endothelin Receptor Antagonists

The most robust data supporting pharmacologic therapy for the treatment of portopulmonary hypertension appears to be with endothelin receptor antagonists. However, these agents are hepatically metabolized and are known to cause hepatotoxicity, so caution must be used in a patient with hepatic impairment.

Bosentan has been associated with an improvement in symptoms in a retrospective study of patients with portopulmonary hypertension [103]. This study also completed a subset pharmacokinetic analysis of five patients with moderate hepatic impairment. The analysis showed an increase in bosentan exposure in this specific patient population; however, this was not related to patient outcomes. One of the major concerns associated with the use of bosentan is its potential to cause liver toxicity [104]. In line with this, Savale *et al.* did identify a 5.5% risk of elevated liver enzymes in their retrospective analysis [103]. Based on these data, it is appropriate to use caution when imitating this agent in patients with hepatic impairment given the increase risk for elevated bosentan levels. Frequent liver function monitor is also clinically appropriate in this patient population.

Macitentan has the most robust data supporting its use in the pulmonary arterial hypertension patient population in the form of a randomized controlled trial showing statistically significant improvement in morbidity and mortality [105]. In regards to the safety of this agent, this study found that there was no variation in liver function abnormalities between varying doses in patients with hepatic dysfunction. However, it is still recommended to obtain liver function tests at base-



line and repeated periodically during the first six months and then as clinically indicated [106].

Ambrisentan has been evaluated in a small prospective, observational, cohort study of portopulmonary hypertension, showing positive outcomes in pulmonary hemodynamics [107]. In regards to safety outcomes, this study did not identify any change in liver function tests throughout the twelve month study period. This would indicate the likelihood that ambrisentan can safely be used in patients with hepatic impairment, however, patients should be closely monitored for adverse effects.

As a whole, the endothelin-receptor antagonist group appears to have decent support for use in the portopulmonary hypertension patient population. It is prudent to monitor these patients for not only hemodynamic adverse effects, but also for direct liver injury indicated by an elevation in liver function tests.

---

## 17.5 Renal

Renal dosing adjustments are required for many medications; however, these adjustments are significantly complicated by the pharmacokinetic alterations, particularly fluctuations in distribution and metabolism that occur in patients with hepatic impairment. Patients with an increased Vd secondary to ascites may potentially have a decreased renal clearance of medications given the kidney's decreased access to the medication to be able to clear it. Also, medications that are usually protein bound typically can have a greater renal clearance in patients with hepatic impairment secondary to decreased protein production, and therefore a greater free concentration available for elimination by the kidney.

HRS is a potential complication associated with ESLD. Agents such as midodrine, octreotide and albumin may potentially be used for the treatment of HRS. None of these commonly used agents require dose adjustments based on pharmacokinetic alterations in patients with hepatic impairment.

---

## 17.6 Gastrointestinal

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly prescribed agents for hospitalized ESLD patients. These agents are commonly prescribed for one of two indications: stress ulcer prophylaxis or treatment of gastro-esophageal variceal hemorrhages [9]. Apart from inpatient use, these two classes of medications are readily available as over-the-counter products that patients may be taking without consultation with a prescriber, so it is important to discuss the concerns with these medications with all patients with hepatic impairment.

### 17.6.1 Proton Pump Inhibitors

There is no evidence to date to recommend one PPI over another for any indication. However, secondary to the fact that most PPIs undergo CYP metabolism, pharmacokinetic alterations caused by hepatic impairment may warrant the selection of one agent over the others.

#### 17.6.1.1 Omeprazole

As one of the oldest available PPIs, omeprazole is a commonly used agent. However, caution is necessary when prescribing this agent for patients with hepatic impairment. In a pharmacokinetic analysis of omeprazole in patients with cirrhosis, it was found that omeprazole exposure was increased regardless of the severity of hepatic impairment [17]. These data would suggest that omeprazole has significantly decreased clearance in the ESLD patient and should likely be avoided if possible.

#### 17.6.1.2 Esomeprazole

A small pharmacokinetic evaluation of esomeprazole in patients with hepatic impairment has been described by Sjövall and colleagues [108]. This study identified a minimal risk of increased esomeprazole exposure in patients with mild or moderate hepatic impairment. However, increase drug levels were noted to be significantly elevated in patients with severe hepatic dysfunction. This concern has been noted by the drug manufacturer, such that in patients with severe hepatic impairment, a dose reduction to 20 mg daily is recommended [109]. Therefore, dosing recommendations remain unchanged for patients with mild to moderate hepatic impairment, but caution should be executed when prescribing esomeprazole for patients with severe hepatic impairment.

#### 17.6.1.3 Lansoprazole

The pharmacokinetics of lansoprazole was evaluated in a single-dose study, which the results are significantly limited by the lack of repeat dosing [110]. It was found that there is an increase in half-life and drug exposure with increase severity of liver disease. Patients with severe hepatic impairment were found to have marked changes in the pharmacokinetic profile. These data suggest that lansoprazole should likely be avoided in patients with hepatic impairment, particularly in patients with severe hepatic impairment.

#### 17.6.1.4 Pantoprazole

Although pantoprazole undergoes CYP metabolism, it has been shown that the pharmacokinetics and tolerability of pantoprazole are similar independent of the severity of hepatic impairment [111]. Therefore, it is unnecessary to dose adjust pantoprazole regardless of the degree of hepatic impairment. This evidence makes pantoprazole the most favorable PPI for use in patients with ESLD.

## 17.6.2 Histamine-2 Receptor Antagonists

Famotidine appears to have a more favorable pharmacokinetic profile in this patient population in comparison to ranitidine. In one pharmacokinetic evaluation of famotidine use in the ESLD patient population, famotidine clearance was unchanged compared to those patients without hepatic impairment [112]. However, famotidine does require dose adjustments for renal impairment, such that patients with HRS should be appropriate dose reduced [113]. Ranitidine has documented increased neuropsychiatric complications in patients with ESLD and should likely be avoided in this patient population [114].

## 17.6.3 Anti-emetics

Decreased gastrointestinal motility, nausea, and vomiting are also common complications associated with ESLD [115].

### 17.6.3.1 Metoclopramide

Metoclopramide is a commonly used agent given its pro-motility and antiemetic effects. However, given the fact that metoclopramide is subject to first-pass metabolism, has significant plasma protein binding properties and undergoes significant hepatic metabolism, dose reductions should be considered in the ESLD patient population [116–120]. Also, given metoclopramide's renal clearance property, a dose reduction is also crucial in patients with concomitant renal dysfunction. A 50% dose reduction is appropriate in patients with cirrhosis.

### 17.6.3.2 Ondansetron

Ondansetron is mainly eliminated via hepatic metabolism [121]. Clearance of ondansetron is related to the degree of hepatic impairment, such that worsening liver impairment leads to significantly decreased ondansetron clearance [122]. Caution should be used when prescribing ondansetron in patients with hepatic impairment. It can also be recommended that for patients with severe hepatic impairment daily doses of ondansetron should be limited to 8 mg.

---

## 17.7 Hematology

### 17.7.1 Venous Thromboembolism Prophylaxis and Anticoagulation

Historically, the endogenous coagulopathy in patients with ESLD due to decreased production of vitamin K clotting factors and platelets was thought to be protective against the development of venous thromboembolism (VTE) [123]. More recent studies have called this theory of “autoantico-

agulation” into question and demonstrated that these patients also have decreased production of anticoagulation factors and may actually be at an increased or similar risk of VTE compared to hospitalized patients without ESLD [124]. Literature evaluating the safety of pharmacologic prophylaxis in ESLD is limited but does raise concern for an increased risk of bleeding complications [125, 126]. In addition, evidence-based VTE prophylaxis guidelines provide no specific recommendations for patients with liver disease but advise against the use of pharmacologic prophylaxis in patients with significant bleeding risk which includes risk factors such as platelet count  $<50,000/\mu\text{L}$ , liver failure, and international normalized ratio (INR)  $>1.5$  [127]. It should be noted that there are limited data in critically ill cirrhotic patients. A recent retrospective study of 798 patients found that the incidence of VTE in critically ill cirrhotic patients was not statistically different from that in noncirrhotic patients although rates were relatively low at 2.7% and 7.6%, respectively. Cirrhotic patients were less likely to receive pharmacologic prophylaxis [128]. ESLD and associated coagulopathy (elevation in INR) alone should not be considered a contraindication to pharmacologic prophylaxis and critically ill patients with ESLD should receive pharmacologic prophylaxis as a default unless there are specific contraindications. Certainly, careful evaluation of risk versus benefit should be done on a patient-by-patient basis.

As a result of the increased risk of VTE, anticoagulation therapy is being increasingly utilized in patients with ESLD. There are limited data on the safety of therapeutic anticoagulation in the hospital setting in patients with ESLD, especially in critically ill patients.

If pharmacologic prophylaxis or therapeutic anticoagulation is initiated with unfractionated heparin there are no dosing considerations specific to patients with liver dysfunction. Many of these patients will have concomitant renal dysfunction and given that low molecular weight heparins (with the exception of dalteparin) are renally eliminated, they present a higher risk for bleeding complications.

Patients with ALF and ACLF frequently have an acute coagulopathy and elevated INR from baseline and are at high risk of bleeding complications. There are no data evaluating the use of VTE prophylaxis or therapeutic anticoagulation in this population. Mechanical prophylaxis only should be recommended during the acute phase of the disease process.

### 17.7.2 Heparin-Induced Thrombocytopenia

The development of heparin-induced thrombocytopenia (HIT) in a patient with liver disease presents a complex situation because evidence-based guidelines recommend therapeutic anticoagulation for four weeks in the setting of isolated HIT without thrombosis and for three months if

there is associated thrombosis [129]. Of course, the increased risk of thrombosis associated with HIT would have to be balanced with the risk of bleeding in order to make a decision about therapeutic anticoagulation in individual patients. Of the medications that would be used for initial anticoagulation in the setting of HIT, argatroban is the only one with pharmacologic considerations in liver dysfunction. Argatroban is a direct thrombin inhibitor that is hepatically metabolized primarily by CYP3A4/5 to non-active metabolites. The elimination half-life is approximately 45 min in healthy volunteers but is increased by threefold in patients with moderate hepatic impairment (Child-Pugh score > 6) along with a fourfold decrease in systemic clearance. Furthermore, anticoagulant responses returned to baseline in 2–4 h in healthy volunteers but took at least six hours (up to 20 h) in patients with hepatic impairment [130]. As a result, the recommended starting dose of argatroban per the manufacturer is decreased from 2 to 0.5 mcg/kg/min in patients with moderate or severe hepatic impairment [126]. A retrospective study supporting this reduced starting dose also recommended delaying the monitoring of the activated partial thromboplastin time (aPTT) to at least four to five hours after initiation or dose adjustments (compared with the standard of two hours) due to the longer time required to achieve steady state concentrations [131]. Retrospective studies of argatroban in critically ill patients describe significantly reduced dosing requirements [132, 133]. One study found a 57% reduction in dose compared with non-critically ill patients and that dose requirements were inversely related to Sequential Organ Failure Assessment (SOFA) score [132]. The authors of a second study in patients with multiple organ dysfunction syndrome (MODS) again found markedly reduced dose requirements but additionally, found a significantly lower mean argatroban dose in patients with hepatic insufficiency than in those without [133]. Accordingly, a starting dose of one tenth to one eighth of the standard starting dose is recommended for critically ill patients with MODS. To reduce the risk of bleeding complications, consideration should be given to the selection of alternative agents in patients with significant hepatic dysfunction. However, if argatroban is utilized in this patient population, a starting dose at the low end of this range is advised (e.g. 0.125 mcg/kg/min).

## 17.8 Infectious Disease

Infection in ESLD is associated with significant morbidity and mortality, including the development of ACLF [134]. In fact, patients with cirrhosis who develop infections have been found to have a fourfold increase in mortality compared to similar patients with cirrhosis without infection [135]. Infection either exists on admission or is acquired during hospitalization in approximately 25–30% of patients with ESLD

which is four to five times higher than the general population [136, 137]. Independent risk factors for infection in patients with cirrhosis include previous infection in the past 12 months, a MELD score of 15 or greater, and protein malnutrition [138]. Patients with both ALF and ESLD are at significant risk of various types of infections although spontaneous bacterial peritonitis (SBP) and urinary tract infections are most common [136, 137, 139–141]. As in the general ICU population, multi-drug resistant (MDR) pathogens are of increasing prevalence in ESLD and should be taken into consideration when selecting antibiotics for nosocomial infections [136]. As a result of the increased incidence of infection as well as the risk of MDR bacteria, utilization of antimicrobials, including broad-spectrum agents, in this patient population is significant. Hepatic dysfunction affects several pharmacokinetic parameters which impacts antimicrobial dosing, including decreased protein binding, metabolism, and renal elimination. As previously mentioned, a significant portion of these patients will have concomitant renal dysfunction which will impact the dosing of the majority of antimicrobials. In contrast to the available literature to guide dosing of antimicrobials in renal dysfunction, there is a shortage of literature on the pharmacokinetics of antimicrobials in liver dysfunction. The antimicrobials used in the ICU that have specific dosing recommendations in the package labeling based on Child-Pugh score are limited to metronidazole, tigecycline, caspofungin, and voriconazole. A recently published review extensively evaluated the pharmacokinetic literature for commonly used antibiotics that undergo hepatic or mixed renal-hepatobiliary clearance [142]. In addition, to noting recommendations that exist in product labeling, the authors make additional dose adjustment recommendations by Child-Pugh score based on the available pharmacokinetic literature. Antibiotics that have recommendations for dose adjustments which are pertinent to the ICU setting include clindamycin, metronidazole, nafcillin, rifampin, and tigecycline. Clindamycin should have a 50% dose reduction in Child-Pugh class C. The dosing interval for metronidazole 500 mg dosing should be changed from every 8 h to every 12–24 h for all Child-Pugh classes. It's noted that nafcillin likely needs a dose adjustment although no specific recommendations are provided. For rifampin, a 50% dose reduction should be considered in all Child-Pugh classes. Finally, a 50% dose reduction should be made for tigecycline in Child-Pugh class C.

Recent literature has highlighted the inadequacy of standard antibiotic dosing regimens in the critically ill. Specifically, the ability to achieve desired concentrations is decreased which has been associated with adverse patient outcomes [143]. It is well known that both ESLD and critical illness are associated with increased Vd, therefore hydrophilic drugs, such as  $\beta$ -lactam antibiotics, are of concern due to the risk of decreased plasma concentrations and thus efficacy. Increased loading doses should be considered [144].

In addition, ESLD has been reported to be a risk factor for several antibiotic related toxicities including  $\beta$ -lactam-induced neutropenia and aminoglycoside-related nephrotoxicity [145, 146].

## 17.9 Endocrine

The incidence of nonalcoholic steatohepatitis (NASH) continues to grow and is one of the most common etiologies of liver cirrhosis [147]. Its growth parallels the global increase in diabetes mellitus (DM), obesity, and metabolic syndrome [147]. Endocrine abnormalities are common, and often significant, in patients with liver disease because the liver is the predominant organ responsible for the metabolism and catabolism of many proteins, hormones, cytokines, and interleukins [148]. In many cases these abnormalities are associated with worse outcomes and necessitate pharmacotherapeutic intervention for the management of DM, thyroid disorder, and relative adrenal insufficiency (RAI).

### 17.9.1 Glycemic Control

Diabetes mellitus is associated with increased risk of hepatic complications, including encephalopathy, portal hypertension, ascites, SBP, renal dysfunction, hepatocellular cancer, and death, in patients with chronic liver disease and cirrhosis [149]. It is thought that DM may promote inflammation and fibrosis via increased mitochondrial oxidative stress, mediated by adipokines. Effective glycemic control may mitigate the development of these adverse effects, though outcome data are lacking [149]. Intensive glycemic control (serum glucose 80–110 mg/dL) has been evaluated during critical illness and was found to significantly increase the risk of hypoglycemia and conferred no overall mortality benefit [150]. Specific to patients with acute decompensated cirrhosis, hypoglycemia is associated with increased mortality, and intraoperative hypoglycemia may also be indicative of post-hepatectomy liver failure [151, 152]. It has not been established whether hypoglycemia is partly responsible for the increased short-term mortality of patients with acute decompensated liver cirrhosis or rather merely a consequence of the severity of the disease or its complications. Nevertheless, conservative management dictates the avoidance of treatments associated with increased hypoglycemia risk. As such, the American Diabetes Association recommends that insulin therapy be initiated for treatment of persistent hyperglycemia, starting at a threshold of 180 mg/dL and titrated to a target glucose range of 140–180 mg/dL for the majority of critically ill patients [153]. While patients with liver failure are not specifically addressed by these guidelines, it is reasonable to

apply these recommendations to that patient population. An insulin infusion has been shown to be the best method for achieving glycemic targets; therapy should be initiated with an intravenous insulin infusion using a validated written or computerized protocol that allows for predefined adjustments in the infusion rate, followed by a transition to “sliding scale” insulin when clinically appropriate. Patients with liver disease may initially require higher doses of insulin to control serum glucose because of insulin resistance in muscle, liver, and adipose [154]. However, as the disease progresses and metabolic function deteriorates, insulin requirements may decrease as gluconeogenesis slows. Oral agents are not ideal for chronic management and are contraindicated in the acute management of DM; they are often hepatically metabolized and can therefore accumulate in these patients and cause toxicity, including hypoglycemia and lactic acidosis [149, 153, 154]. DM is difficult to manage in patients with liver disease, given that both hyper- and hypo-glycemia are associated with poor outcomes and close clinical monitoring is warranted.

### 17.9.2 Thyroid

The liver is primarily responsible for the peripheral conversion of tetraiodothyronine (T<sub>4</sub>) to triiodothyronine (T<sub>3</sub>), as well as the synthesis of many proteins, including thyroid binding proteins. Therefore, dysregulation and dysfunction of thyroid hormones are anticipated in patients with cirrhosis [148, 155]. The incidence of thyroid abnormalities in the setting of liver disease is variable, ranging from 13 to 61%. Hypothyroidism is most common and presents most frequently as low T<sub>3</sub> and low free T<sub>3</sub>, although hyperthyroidism can also occur [155, 156]. In the critically ill cirrhotic patient admitted to the ICU, more than half had some form of Euthyroid Sick Syndrome [157]. While thyroid dysfunction has been associated with decreased short- and long-term survival of patients with liver cirrhosis, data are not conclusive [158]. A retrospective study found that liver function in patients with a hypothyroid state tended to be better than in those with a euthyroid state [159]. Given that the appropriate treatment of Euthyroid Sick Syndrome is unclear in patients with normal liver function, the additional layer of complexity imposed by liver dysfunction, along with inconclusive outcome data, makes it difficult to establish a treatment plan. Additionally, levothyroxine has been associated with an increased risk of hypoglycemia in patients with liver impairment [160]. The pharmacokinetic profile of levothyroxine is not significantly altered by liver disease, but given our understanding of the consequences of hypoglycemia in this patient population, conservative thyroid management is warranted.



### 17.9.3 Adrenal Insufficiency

RAI, sometimes referred to as hepatoadrenal syndrome, is common in critically ill patients, but it also has been reported in patients with uncompensated and stable cirrhosis, including those with and without septic shock [148, 161–163]. The reported incidence is variable, ranging from 7.2 to 60%, in part due to wide variability in laboratory technique and test criteria used for diagnosis [148, 164, 165]. Despite this variability, most studies have demonstrated RAI to be associated with poor prognosis in cirrhotic patients. A relationship appears to exist between the severity of the liver disease and the presence of RAI, though neither the mechanism nor the exact prevalence of RAI is fully understood [161, 163]. The diagnosis of RAI also remains controversial. Meta-analyses have evaluated the role of low- (1 mcg) and standard-dose (250 mcg) corticotropin test in the diagnosis of RAI, finding that both tests performed well but were not without limitations [166, 167]. Endocrine Society Guidelines recommend the use of standard-dose (250 mcg) corticotropin as the “gold standard” diagnostic tool to establish the diagnosis, although liver disease affects how the test is interpreted. Alterations in serum free and total cortisol levels have been observed in both chronic and severe acute hepatitis as a result of decreased protein binding [168, 169]. Serum free cortisol or free cortisol index may be preferred for the evaluation of RAI compared to serum total cortisol in these patients [168, 169]. Guidelines recommend the use of a low diagnostic (and therapeutic) threshold in acutely ill patients, as well as in patients with predisposing factors, such as liver disease [170]. A few studies have evaluated the role of corticosteroids in the treatment of RAI in patients with liver cirrhosis, with and without septic shock [159, 162, 163, 171, 172]. For all studies the intervention was hydrocortisone dosed at 200–300 mg per day, sometimes referred to “stress-dose”, with outcomes focused on vasopressor dose and duration, shock resolution, shock recurrence, adverse effects including infection and gastrointestinal bleed, and hospital survival. Outcome data are mixed, as are expert opinions, similar to the data set and expert opinions representative of septic patients without liver cirrhosis. Endocrine guidelines recommend fludrocortisone 0.1 mg daily and hydrocortisone 15–25 mg given two to three times daily in adults with RAI, though this is a broad recommendation and not specific to patients with liver disease [170]. This dose is considerably lower than what has been studied in liver cirrhosis, and what is recommended by the Surviving Sepsis Guidelines (hydrocortisone 200 mg daily) [173]. The dose of hydrocortisone need not be adjusted in patients with liver failure. Additional high-quality data are needed to make strong recommendations, though the administration of glucocorticoids, and perhaps mineralocorticoids, may improve outcomes in patients with liver cirrhosis, including when accompanied by septic shock.

### 17.10 Special Populations

#### 17.10.1 Continuous Renal Replacement Therapy

There is a potential for critically ill patients with hepatic impairment to require continuous renal replacement therapy (CRRT). Dose adjustments are commonly necessary for medications with specific pharmacokinetic properties [174] (Table 17.3). It is critical to understand that these properties may be significantly altered from baseline in patients with hepatic impairment. Medication clearance is also significantly influence by CRRT modality and effluent rate. In order to appropriately dose medications in patient with hepatic impairment receiving CRRT, critical evaluation of each medication’s pharmacokinetic properties in relation to both hepatic clearance and CRRT clearance is essential.

#### 17.10.2 Extracorporeal Liver Support Systems

Accumulation of various toxins that otherwise would be metabolized by the liver contribute to many of the complications seen in ALF and ACLF. Several of these toxins (e.g. ammonia and endogenous benzodiazepines) are involved in some of the most significant manifestations of ALF and ACLF, cerebral edema and hepatic encephalopathy, respectively. Others (e.g. pro-inflammatory cytokines) may play a role in cardiovascular and renal dysfunction.

Extracorporeal liver support (ECLS) systems, or liver assist devices, can act as a bridge to liver recovery (since the liver can maintain the ability to regenerate, especially in ALF) or liver transplantation by mimicking the function of the liver and assisting with various hepatic functions. There are two types of ECLS systems: artificial and bioartificial. Artificial systems eliminate albumin-bound and water soluble substances, including bilirubin and various toxins, with technologies utilizing exogenous albumin and artificial membranes similar to those used in hemodialysis. Examples of artificial systems include the Molecular Adsorbent Recirculating System (MARS [Teraklin AG, Rostock, Germany]), single-pass albumin dialysis (SPAD), Prometheus (Fresenius, Hamburg, Germany), and high-volume plasmapheresis (HVP). Bioartificial systems differ because they use living hepatocytes and therefore provide some synthetic and metabolic function in addition to detoxification. Examples of bioartificial

**Table 17.3** Example of some drug attributes to increase likelihood of removal via CRRT

Drug attribute
Low percent protein binding
Small volume of distribution
Small molecular weight

systems include the Extracorporeal Liver Assist Device (ELAD, Vital Therapies, Inc., San Diego, USA) and HepatAssist (Arbios, USA). MARS is the most frequently used ECLS system in the United States as well as the most extensively studied, although HVP is the only ECLS system to demonstrate an improvement in transplant-free survival in ALF thus far [175]. Study outcomes related to the use of ECLS systems in both ALF and ACLF have been recently extensively reviewed [176].

### 17.10.2.1 Drug Considerations

Given that artificial ECLS systems eliminate albumin-bound and water soluble substances, removal of drugs which have these qualities is a special consideration in determining appropriate dosing. In addition, timing of the administration of the drugs in relation to the timing of ECLS system treatment can have a significant impact on drug removal. Since MARS is the most commonly used ECLS system in the United States, this section will focus on drug dosing considerations during MARS and will review the available pharmacokinetic data for drugs utilized in the ICU. MARS employs albumin dialysis to remove both albumin bound and water soluble substances. It should be noted that MARS is used in conjunction with CRRT (see the chapter entitled *Use of Extra-corporeal Liver Support Therapies* for detailed information regarding MARS mechanisms and system set-up). Drugs can be removed by the MARS system in addition to clearance from CRRT making dosing complicated. Also, drugs with both high and low protein binding can be removed given the two different mechanisms of removal. There is very little literature describing the impact of MARS on drug removal and therefore very little guidance on appropriate dosing.

One study utilized an *in vitro* model to examine the effects of MARS on the removal of several different drugs with varying pharmacokinetic characteristics compared with removal via continuous venovenous hemodialysis (CVVHD) [177]. Ceftriaxone (low Vd) and teicoplanin (high Vd) are both highly albumin bound antibiotics. Ceftriaxone concentrations decreased by 71% in 6 h with MARS compared with 20% with CVVHD. Similarly, teicoplanin concentrations decreased by 90% with MARS and 58% with CVVHD which demonstrates significant removal via both therapies. Both ceftazidime (low Vd) and levofloxacin (high Vd) have negligible albumin binding and as a result were shown to have similar removal during MARS and CVVHD which was primarily driven by CVVHD clearance. Ceftazidime concentrations decreased by 98.4% in CVVHD and 99.8% in MARS. Likewise, levofloxacin concentrations decreased by 99.3% in both CVVHD and MARS.

A second study also using an *in vitro* model described the removal of moxifloxacin and meropenem [178]. Moxifloxacin is moderately albumin-bound and meropenem demonstrates low albumin binding. The concentrations of both moxifloxa-

cin and meropenem decreased by approximately 50% 1 h after the initiation of MARS. Both medications were found in all portions of the MARS system as well as the dialysate demonstrating removal by the MARS component as well as the dialysis component.

Piperacillin-tazobactam removal during MARS has also been described in two case reports [179, 180]. In one case report, a patient receiving MARS for APAP-induced ALF received a single dose of piperacillin-tazobactam 4.5 gm administered over three hours [180]. Piperacillin-tazobactam is known to be cleared via CRRT and is moderately protein bound. Piperacillin concentrations decreased by approximately 32% from one hour after the end of the infusion to three hours later. The half-life was calculated to be 1.53 h which was 3.7-fold shorter than that reported with CVVHD alone demonstrating additional removal via MARS [181]. In the second case report, one patient received MARS for refractory hepatic encephalopathy and a second patient received MARS for hepatic failure (including encephalopathy) after hepatectomy [179]. The first patient had piperacillin concentrations measured after the first dose of 3.375 gm administered over four hours. The second patient had piperacillin concentrations measured during two different three-hour extended infusion piperacillin-tazobactam dosing regimen: 4.5 gm every 8 h and 3.375 gm every 8 h. All serum concentrations taken from both patients (including at the end of MARS therapy and the dosing interval) exceeded that which would be desired for treatment of the involved organisms per the MIC breakpoints recommended by the 2014 Clinical Laboratory Standards Institute guidelines [182].

One case report describes negligible removal of tacrolimus during MARS despite the fact that it has a low-molecular weight and is highly protein-bound [183]. Finally, MARS has been used for the management of acute poisoning from a variety of drugs and substances which has been recently extensively reviewed [184].

Clinicians should anticipate significant removal of any highly protein bound drug during MARS treatment sessions and ideally time the administration of those drugs for after MARS treatment sessions are complete if using intermittent sessions. Using extended or continuous infusion times could be considered for certain drugs, especially if MARS is being run continuously. Utilizing therapeutic drug monitoring when available can provide significant guidance on appropriate dosing given the lack of pharmacokinetic data.

### 17.10.3 Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO), which often requires therapeutic anticoagulation with mechanical support, is not common in the context of liver

failure due to its association with underlying coagulopathy, but when employed it poses an additional layer of complexity for drug dosing. Several mechanisms account for alternations in pharmacokinetic parameters during ECMO. The larger apparent  $V_d$ , as a product of larger circulatory volume, disproportionately affects drugs with small  $V_d$  (hydrophilic) and thereby results in lower maximum concentration ( $C_{max}$ ) and increased elimination [185]. Furthermore, this may be complicated by ongoing fluid removal either via forced diuresis or CRRT, which results in a dynamic  $V_d$  and variable drug concentrations. Drug inactivation, sequestration, or adsorption by the various components of the ECMO circuit also influences pharmacokinetics. The  $V_d$ , degree of protein binding, and the extent of equilibrium between tissue and plasma concentration upon initiation of ECMO will dictate the degree of pharmacologic impact ECMO has on these drugs [185–190].

Patients requiring ECMO often necessitate increased analgesic and sedative doses, including morphine, fentanyl, and midazolam [185, 190, 191]. This may be in part due to the deeper sedation goals to optimize oxygenation and minimize agitation-related sequelae such as ECMO circuit complications, but it is also related to pharmacokinetic changes during ECMO. While analgesics, sedatives, inotropes, vasopressors, diuretics, and anticoagulants may be titrated to measurable endpoints, no real time target exists for antibiotics [192]. Due to the multiple variables that may influence the pharmacokinetic profile of drugs in critically ill patients, drug regimens should be individualized. Initial doses should be based on population pharmacokinetics and increased frequency of therapeutic drug monitoring with subsequent adjustments should be employed whenever possible [185, 192, 193].

### Conclusion

The management of a chronic disease complicated by an acute exacerbation is challenging enough without having to consider potential clinically important changes in the pharmacokinetics and pharmacodynamics of drug therapy. In the context of liver disease, the drugs used to treat the condition are altered significantly by the disease itself and can further complicate drug therapy. Avoidance of some drugs and dose adjustments in others are necessary to avoid drug misadventures and further deterioration of an already fragile disease state. Basic considerations for drug therapy have been reviewed, including a deeper assessment organized by organ system. Additionally, consideration has been given to devices that will further alter the pharmacokinetics and pharmacodynamics in the setting of liver disease. Drug therapy should be based on evidence-based outcome data, and guidelines when available, along with the side effect profile of a given medication. Dosing of medications in patients with liver disease should be based on population kinetics in patients with

liver disease, and not extrapolated from other patient populations. When possible, therapeutic drug monitoring should be implemented and therapy should be customized to each individual patient.

## 17.11 Chapter Assessment Questions (Bold Emphasis Answers are Correct)

- Which of the following best describes the effect of acute liver failure (ALF) on drug distribution?  
**Increased volume of distribution**  
 Decreased volume of distribution  
 Increase in protein binding  
 Decrease in the fraction of free drug available
- Which of the following sedative agents appears to be the safest agent to use in patients with ESLD?  
 Dexmedetomidine  
 Lorazepam  
 Midazolam  
**Propofol**
- Based on medication half-life, which synthetic prostacyclin does not require cautious dosing or dose adjustments for the treatment of portopulmonary hypertension?  
 Bosentan  
**Epoprostenol**  
 Iloprost  
 Treprostinil
- Which of the following beta-blockers should be dosed cautiously in patients with ALF secondary to increased bioavailability, area-under-the-curve, and elimination half-life?  
 Esmolol  
**Metoprolol**  
 Nadolol  
 Propranolol
- Which proton pump inhibitor does NOT require dose adjustments in patients with severe ESLD?  
 Esomeprazole  
 Lansoprazole  
 Omeprazole  
**Pantoprazole**
- Which of the following statements is true regarding pharmacologic venous thromboembolism prophylaxis in patients with end-stage liver disease (ESLD)?  
 Autoanticoagulation in ESLD negates the need for pharmacologic prophylaxis.  
**ESLD and associated coagulopathy alone should not be considered a contraindication to pharmacologic prophylaxis and critically ill patients with ESLD should receive pharmacologic prophylaxis as a default unless there are specific contraindications.**

Evidence supports that ESLD patients should only receive pharmacologic prophylaxis if the platelet count is greater than 100,000/ $\mu$ L and the INR is less than 2.5.

Low-molecular weight heparin prophylaxis is the preferred agent for pharmacologic prophylaxis in all ELSL patients.

7. Which of the following antimicrobial medications requires a 50% dose reduction for all classifications of Child Pugh classes?

Clindamycin

Metronidazole

**Rifampin**

Tobramycin

8. What pharmacokinetic properties make a medication likely to be removed via continuous renal replacement therapy (CRRT)?

Large volume of distribution, high protein binding, large molecular weight

Large volume of distribution, low protein binding, large molecular weight

Small volume of distribution, high protein binding, small molecular weight

**Small volume of distribution, low protein binding, small molecular weight**

## References

- Lin S, Smith BS. Drug dosing considerations for the critically ill patient with liver disease. *Crit Care Nurs Clin North Am.* 2010;22(3):335–40. Epub 2010/08/10
- Delco F, Tchambaz L, Schlienger R, Drewe J, Krahenbuhl S. Dose adjustment in patients with liver disease. *Drug Saf.* 2005;28(6):529–45. Epub 2005/06/01
- Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol.* 2008;64(12):1147–61. Epub 2008/09/03
- Chalasani N, Gorski JC, Patel NH, Hall SD, Galinsky RE. Hepatic and intestinal cytochrome P450 3A activity in cirrhosis: effects of transjugular intrahepatic portosystemic shunts. *Hepatology.* 2001;34(6):1103–8. Epub 2001/12/04
- Gorski JC, Jones DR, Haehner-Daniels BD, Hamman MA, O'Mara EM Jr, Hall SD. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther.* 1998;64(2):133–43. Epub 1998/09/05
- el Touny M, el Guinaidy M, Abdel Bary M, Osman L, Sabbour MS. Pharmacokinetics of cefodizime in patients with liver cirrhosis and ascites. *Chemotherapy.* 1992;38(4):201–5. Epub 1992/01/01
- MacKichan J. Influence of protein binding and use of unbound (free) drug concentrations. In: Burton M, Shaw LM, Schentag JJ, Evans WE, editors. *Applied pharmacokinetics & pharmacodynamics—principles of therapeutic drug monitoring.* Philadelphia: Lipponcott Williams & Wilkins; 2006. p. 82–120.
- Elbekai RH, Korashy HM, El-Kadi AO. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. *Curr Drug Metab.* 2004;5(2):157–67. Epub 2004/04/14
- Albarmawi A, Czock D, Gauss A, Ehehalt R, Lorenzo Bermejo J, Burhenne J, et al. CYP3A activity in severe liver cirrhosis correlates with Child-Pugh and model for end-stage liver disease (MELD) scores. *Br J Clin Pharmacol.* 2014;77(1):160–9. Epub 2013/06/19
- Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):263–306. Epub 2012/12/28
- Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc.* 2010;85(5):451–8. Epub 2010/04/02
- Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault PF, et al. Impact of systematic evaluation of pain and agitation in an intensive care unit. *Crit Care Med.* 2006;34(6):1691–9. Epub 2006/04/21
- Payen JF, Bosson JL, Chanques G, Mantz J, Labarere J, Investigators D. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. *Anesthesiology.* 2009;111(6):1308–16. Epub 2009/11/26
- Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137(12):947–54. Epub 2002/12/18
- Rossi S, Assis DN, Awsare M, Brunner M, Skole K, Rai J, et al. Use of over-the-counter analgesics in patients with chronic liver disease: physicians' recommendations. *Drug Saf.* 2008;31(3):261–70. Epub 2008/02/28
- Bosilkovska M, Walder B, Besson M, Daali Y, Desmeules J. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. *Drugs.* 2012;72(12):1645–69. Epub 2012/08/08
- Dwyer JP, Jayasekera C, Nicoll A. Analgesia for the cirrhotic patient: a literature review and recommendations. *J Gastroenterol Hepatol.* 2014;29(7):1356–60. Epub 2014/02/20
- Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology.* 2005;42(6):1364–72. Epub 2005/12/01
- Khalid SK, Lane J, Navarro V, Garcia-Tsao G. Use of over-the-counter analgesics is not associated with acute decompensation in patients with cirrhosis. *Clinical Gastroenterol Hepatol.* 2009;7(9):994–9. quiz 13–4. Epub 2009/04/28
- Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology.* 1995;22(3):767–73. Epub 1995/09/01
- Gallagher J, Biesboer AN, Killian AJ. Pharmacologic Issues in Liver Disease. *Crit Care Clin.* 2016;32(3):397–410. Epub 2016/06/25
- Imani F, Motavaf M, Safari S, Alavian SM. The therapeutic use of analgesics in patients with liver cirrhosis: a literature review and evidence-based recommendations. *Hepat Mon.* 2014;14(10):e23539. Epub 2014/12/06
- Soleimanpour H, Safari S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: a systematic review. *Hepat Mon.* 2016;16(4):e32636. Epub 2016/06/04
- Yogarathnam D, Ditch K, Medeiros K, Miller MA, Smith BS. The impact of liver and renal dysfunction on the pharmacokinetics and pharmacodynamics of sedative and analgesic drugs in critically ill adult patients. *Crit Care Nurs Clin North Am.* 2016;28(2):183–94. Epub 2016/05/25
- Carson JL, Strom BL, Duff A, Gupta A, Das K. Safety of nonsteroidal anti-inflammatory drugs with respect to acute liver disease. *Arch Intern Med.* 1993;153(11):1331–6. Epub 1993/06/14
- Fry SW, Seeff LB. Hepatotoxicity of analgesics and anti-inflammatory agents. *Gastroenterol Clin N Am.* 1995;24(4):875–905. Epub 1995/12/01



27. Horl WH. Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals*. 2010;3(7):2291–321. Epub 2010/07/21
28. Ackerman Z, Cominelli F, Reynolds TB. Effect of misoprostol on ibuprofen-induced renal dysfunction in patients with decompensated cirrhosis: results of a double-blind placebo-controlled parallel group study. *Am J Gastroenterol*. 2002;97(8):2033–9. Epub 2002/08/23
29. Boyer TD, Zia P, Reynolds TB. Effect of indomethacin and prostaglandin A1 on renal function and plasma renin activity in alcoholic liver disease. *Gastroenterology*. 1979;77(2):215–22. Epub 1979/08/01
30. Brater DC, Anderson SA, Brown-Cartwright D. Reversible acute decrease in renal function by NSAIDs in cirrhosis. *Am J Med Sci*. 1987;294(3):168–74. Epub 1987/09/01
31. Mirouze D, Zipser RD, Reynolds TB. Effect of inhibitors of prostaglandin synthesis on induced diuresis in cirrhosis. *Hepatology*. 1983;3(1):50–5. Epub 1983/01/01
32. Perez-Ayuso RM, Arroyo V, Camps J, Rimola A, Gaya J, Costa J, et al. Evidence that renal prostaglandins are involved in renal water metabolism in cirrhosis. *Kidney Int*. 1984;26(1):72–80. Epub 1984/07/01
33. Planas R, Arroyo V, Rimola A, Perez-Ayuso RM, Rodes J. Acetylsalicylic acid suppresses the renal hemodynamic effect and reduces the diuretic action of furosemide in cirrhosis with ascites. *Gastroenterology*. 1983;84(2):247–52. Epub 1983/02/01
34. Quintero E, Gines P, Arroyo V, Rimola A, Camps J, Gaya J, et al. Sulindac reduces the urinary excretion of prostaglandins and impairs renal function in cirrhosis with ascites. *Nephron*. 1986;42(4):298–303. Epub 1986/01/01
35. De Ledingham V, Heresbach D, Fourdan O, Bernard P, Liebaert-Bories MP, Noursbaum JB, et al. Anti-inflammatory drugs and variceal bleeding: a case-control study. *Gut*. 1999;44(2):270–3. Epub 1999/01/23
36. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesth Analg*. 1987;66(12):1256–63. Epub 1987/12/01
37. Servin F, Cockshott ID, Farinotti R, Haberer JP, Winckler C, Desmonts JM. Pharmacokinetics of propofol infusions in patients with cirrhosis. *Br J Anaesth*. 1990;65(2):177–83. Epub 1990/08/01
38. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology*. 1988;69(6):887–91. Epub 1988/12/01
39. Amoros A, Aparicio JR, Garmendia M, Casellas JA, Martinez J, Jover R. Deep sedation with propofol does not precipitate hepatic encephalopathy during elective upper endoscopy. *Gastrointest Endosc*. 2009;70(2):262–8. Epub 2009/04/28
40. Assy N, Rosser BG, Grahame GR, Minuk GY. Risk of sedation for upper GI endoscopy exacerbating subclinical hepatic encephalopathy in patients with cirrhosis. *Gastrointest Endosc*. 1999;49(6):690–4. Epub 1999/05/27
41. Khamaysi I, William N, Olga A, Alex I, Vladimir M, Kamal D, et al. Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: a randomized controlled study. *J Hepatol*. 2011;54(1):72–7. Epub 2010/10/12
42. Sharma P, Singh S, Sharma BC, Kumar M, Garg H, Kumar A, et al. Propofol sedation during endoscopy in patients with cirrhosis, and utility of psychometric tests and critical flicker frequency in assessment of recovery from sedation. *Endoscopy*. 2011;43(5):400–5. Epub 2011/05/07
43. Agrawal A, Sharma BC, Sharma P, Uppal R, Sarin SK. Randomized controlled trial for endoscopy with propofol versus midazolam on psychometric tests and critical flicker frequency in people with cirrhosis. *J Gastroenterol Hepatol*. 2012;27(11):1726–32. Epub 2012/08/07
44. Lera dos Santos ME, Maluf-Filho F, Chaves DM, Matuguma SE, Ide E, Luz Gde O, et al. Deep sedation during gastrointestinal endoscopy: propofol-fentanyl and midazolam-fentanyl regimens. *World J Gastroenterol*. 2013;19(22):3439–46. Epub 2013/06/27
45. Riphaut A, Lechowicz I, Frenz MB, Wehrmann T. Propofol sedation for upper gastrointestinal endoscopy in patients with liver cirrhosis as an alternative to midazolam to avoid acute deterioration of minimal encephalopathy: a randomized, controlled study. *Scand J Gastroenterol*. 2009;44(10):1244–51. Epub 2009/10/09
46. Weston BR, Chadlawada V, Chalasani N, Kwo P, Overley CA, Symms M, et al. Nurse-administered propofol versus midazolam and meperidine for upper endoscopy in cirrhotic patients. *Am J Gastroenterol*. 2003;98(11):2440–7. Epub 2003/11/26
47. Wong JM. Propofol infusion syndrome. *Am J Ther*. 2010;17(5):487–91. Epub 2010/09/17
48. Bray RJ. Propofol-infusion syndrome in children. *Lancet*. 1999;353(9169):2074–5. Epub 1999/06/22
49. Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care*. 2009;13(5):R169. Epub 2009/10/31
50. Keegan MT, Plevak DJ. Preoperative assessment of the patient with liver disease. *Am J Gastroenterol*. 2005;100(9):2116–27. Epub 2005/09/01
51. Soleimanpour H, Safari S, Rahmani F, Jafari Rouhi A, Alavian SM. Intravenous hypnotic regimens in patients with liver disease; a review article. *Anesthesiol Pain Med*. 2015;5(1):e23923. Epub 2015/03/21
52. Vaja R, McNicol L, Sisley I. Anaesthesia for patients with liver disease. *Contin Educ Anaesth Crit Care Pain*. 2009;10(1):15–9.
53. Schwartz RBSG. *Pharmacologic adjuncts to intubation*. 6th ed. Philadelphia PA: Elsevier; 2014.
54. Dasta JF, Kane-Gill SL, Pencina M, Shehabi Y, Bokesch PM, Wisemandle W, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. *Crit Care Med*. 2010;38(2):497–503. Epub 2009/10/01
55. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151–60. Epub 2012/03/23
56. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298(22):2644–53. Epub 2007/12/13
57. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489–99. Epub 2009/02/04
58. Holliday SF, Kane-Gill SL, Empey PE, Buckley MS, Smithburger PL. Interpatient variability in dexmedetomidine response: a survey of the literature. *ScientificWorldJournal*. 2014;2014:805013. Epub 2014/02/22
59. Valitalo PA, Ahtola-Satila T, Wighton A, Sarapohja T, Pohjanjousi P, Garratt C. Population pharmacokinetics of dexmedetomidine in critically ill patients. *Clin Drug Investig*. 2013;33(8):579–87. Epub 2013/07/11
60. Hospira, Inc. Precedex [package insert]. Lake Forest, IL: Hospira, Inc.; 2016.
61. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002;30(1):119–41. Epub 2002/03/21

62. Swart EL, de Jongh J, Zuideveld KP, Danhof M, Thijs LG, Strack van Schijndel RJ. Population pharmacokinetics of lorazepam and midazolam and their metabolites in intensive care patients on continuous venovenous hemofiltration. *Am J Kidney Dis*. 2005;45(2):360–71. Epub 2005/02/03
63. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM. Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol*. 2004;57(2):135–45. Epub 2004/01/30
64. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM. Population pharmacodynamic modelling of lorazepam- and midazolam-induced sedation upon long-term continuous infusion in critically ill patients. *Eur J Clin Pharmacol*. 2006;62(3):185–94. Epub 2006/01/21
65. Haq MM, Faisal N, Khalil A, Haqqi SA, Shaikh H, Arain N. Midazolam for sedation during diagnostic or therapeutic upper gastrointestinal endoscopy in cirrhotic patients. *Eur J Gastroenterol Hepatol*. 2012;24(10):1214–8. Epub 2012/07/13
66. Lee PC, Yang YY, Lin MW, Hou MC, Huang CS, Lee KC, et al. Benzodiazepine-associated hepatic encephalopathy significantly increased healthcare utilization and medical costs of Chinese cirrhotic patients: 7-year experience. *Dig Dis Sci*. 2014;59(7):1603–16. Epub 2014/02/01
67. MacGilchrist AJ, Birnie GG, Cook A, Scobie G, Murray T, Watkinson G, et al. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut*. 1986;27(2):190–5. Epub 1986/02/01
68. Pentikainen PJ, Valisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol*. 1989;29(3):272–7. Epub 1989/03/01
69. Trouvin JH, Farinotti R, Haberer JP, Servin F, Chauvin M, Duvaldestin P. Pharmacokinetics of midazolam in anesthetized cirrhotic patients. *Br J Anaesth*. 1988;60(7):762–7. Epub 1988/06/01
70. Rang HPDM, Ritter JM, Flower RJ. *Pharmacology*. 6th ed. Edinburgh: Churchill Livingstone; 2007.
71. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet*. 1981;6(2):89–105. Epub 1981/03/01
72. Greenblatt DJ, Shader RI. Pharmacokinetic understanding of anti-anxiety drug therapy. *South Med J*. 1978;71(Suppl 2):2–9. Epub 1978/08/01
73. Wilkinson GR. The effects of liver disease and aging on the disposition of diazepam, chlorthalidoxepoxide, oxazepam and lorazepam in man. *Acta Psychiatr Scand Suppl*. 1978;274:56–74. Epub 1978/01/01
74. Anderson GD, Hakimian S. Pharmacokinetic of antiepileptic drugs in patients with hepatic or renal impairment. *Clin Pharmacokinet*. 2014;53(1):29–49. Epub 2013/10/15
75. Asconape JJ. Use of antiepileptic drugs in hepatic and renal disease. *Handb Clin Neurol*. 2014;119:417–32. Epub 2013/12/25
76. Brockmoller J, Thomsen T, Wittstock M, Coupez R, Lochs H, Roots I. Pharmacokinetics of levetiracetam in patients with moderate to severe liver cirrhosis (Child-Pugh classes A, B, and C): characterization by dynamic liver function tests. *Clin Pharmacol Ther*. 2005;77(6):529–41. Epub 2005/06/18
77. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, et al. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109(7):950–66. quiz 67. Epub 2014/06/18
78. Asconape JJ. The selection of antiepileptic drugs for the treatment of epilepsy in children and adults. *Neurol Clin*. 2010;28(4):843–52. Epub 2010/09/08
79. Ahmed SN, Siddiqi ZA. Antiepileptic drugs and liver disease. *Seizure*. 2006;15(3):156–64. Epub 2006/01/31
80. Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care*. 2008;14(2):189–97. Epub 2008/04/05
81. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877–87. Epub 2008/02/29
82. Runyon BA, Aasld. Introduction to the revised American association for the study of liver diseases practice guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57(4):1651–3. Epub 2013/03/07
83. Klotz U. Antiarrhythmics: elimination and dosage considerations in hepatic impairment. *Clin Pharmacokinet*. 2007;46(12):985–96. Epub 2007/11/22
84. Regardh CG, Jordo L, Ervik M, Lundborg P, Olsson R, Ronn O. Pharmacokinetics of metoprolol in patients with hepatic cirrhosis. *Clin Pharmacokinet*. 1981;6(5):375–88. Epub 1981/09/01
85. Latini R, Tognoni G, Kates RE. Clinical pharmacokinetics of amiodarone. *Clin Pharmacokinet*. 1984;9(2):136–56. Epub 1984/03/01
86. Gill J, Heel RC, Fitton A. Amiodarone. An overview of its pharmacological properties, and review of its therapeutic use in cardiac arrhythmias. *Drugs*. 1992;43(1):69–110. Epub 1992/01/01
87. Kurosawa S, Kurosawa N, Owada E, Soeda H, Ito K. Pharmacokinetics of diltiazem in patients with liver cirrhosis. *Int J Clin Pharmacol Res*. 1990;10(6):311–8. Epub 1990/01/01
88. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27(1):28–34. Epub 1998/01/13
89. Ramalingam VS, Ansari S, Fisher M. Respiratory complication in liver disease. *Crit Care Clin*. 2016;32(3):357–69. Epub 2016/06/25
90. Fix OK, Bass NM, De Marco T, Merriman RB. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. *Liver Transpl*. 2007;13(6):875–85. Epub 2007/06/01
91. Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology*. 1999;30(3):641–8. Epub 1999/08/26
92. Sussman N, Kaza V, Barshes N, Stribling R, Goss J, O'Mahony C, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. *Am J Transpl*. 2006;6(9):2177–82. Epub 2006/06/27
93. Hoepfer MM, Halank M, Marx C, Hoeffken G, Seyfarth HJ, Schauer J, et al. Bosentan therapy for portopulmonary hypertension. *Eur Respir J*. 2005;25(3):502–8. Epub 2005/03/02
94. Reichenberger F, Voswinckel R, Steveling E, Enke B, Kreckel A, Olschewski H, et al. Sildenafil treatment for portopulmonary hypertension. *Eur Respir J*. 2006;28(3):563–7. Epub 2006/06/30
95. Hildebrand M, Krause W, Angeli P, Koziol T, Gatta A, Merkel C, et al. Pharmacokinetics of iloprost in patients with hepatic dysfunction. *Int J Clin Pharmacol Ther Toxicol*. 1990;28(10):430–4. Epub 1990/10/01
96. Actelion Pharmaceuticals, Inc. Veletri [package insert]. South San Francisco, CA: Actelion Pharmaceuticals, Inc.; 2016.
97. United Therapeutics Corp. Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp; 2014.
98. Peterson L, Marbury T, Marier J, Laliberte K. An evaluation of the pharmacokinetics of treprostinil diolamine in subjects with hepatic impairment. *J Clin Pharm Ther*. 2013;38(6):518–23. Epub 2013/09/17
99. Pfizer Labs. Revatio [package insert]. New York, NY: Pfizer Labs; 2014.

100. Pfizer Labs. Viagra [package insert]. New York, NY: Pfizer Labs; 2015.
101. Eli Lilly and Company. Adcirca [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015.
102. Forgue ST, Phillips DL, Bedding AW, Payne CD, Jewell H, Patterson BE, et al. Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol*. 2007;63(1):24–35. Epub 2006/07/28
103. Savale L, Magnier R, Le Pavec J, Jais X, Montani D, O'Callaghan DS, et al. Efficacy, safety and pharmacokinetics of bosentan in portopulmonary hypertension. *Eur Respir J*. 2013;41(1):96–103. Epub 2012/06/02
104. Roustit M, Fonrose X, Montani D, Girerd B, Stanke-Labesque F, Gonnet N, et al. CYP2C9, SLCO1B1, SLCO1B3, and ABCB11 polymorphisms in patients with bosentan-induced liver toxicity. *Clin Pharmacol Ther*. 2014;95(6):583–5. Epub 2014/05/21
105. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809–18. Epub 2013/08/30
106. Acetlion Pharmaceuticals US, Inc. Opsumit [package insert]. South San Francisco, CA: Acetlion Pharmaceuticals US, Inc.; 2016.
107. Cartin-Ceba R, Swanson K, Iyer V, Wiesner RH, Krowka MJ. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. *Chest*. 2011;139(1):109–14. Epub 2010/08/14
108. Kumar R, Chawla YK, Garg SK, Dixit RK, Satapathy SK, Dhiman RK, et al. Pharmacokinetics of omeprazole in patients with liver cirrhosis and extrahepatic portal venous obstruction. *Methods Find Exp Clin Pharmacol*. 2003;25(8):625–30. Epub 2003/12/13
109. AstraZeneca Pharmaceuticals LP. Nexium [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.
110. Delhotal-Landes B, Flouvat B, Duchier J, Molinie P, Dellatolas F, Lemaire M. Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. *Eur J Clin Pharmacol*. 1993;45(4):367–71. Epub 1993/01/01
111. Ferron GM, Preston RA, Noveck RJ, Pockros P, Mayer P, Getsy J, et al. Pharmacokinetics of pantoprazole in patients with moderate and severe hepatic dysfunction. *Clin Ther*. 2001;23(8):1180–92. Epub 2001/09/18
112. Vincon G, Baldit C, Couzigou P, Demotes-Mainard F, Elouaer-Blanc L, Bannwarth B, et al. Pharmacokinetics of famotidine in patients with cirrhosis and ascites. *Eur J Clin Pharmacol*. 1992;43(5):559–62. Epub 1992/01/01
113. Merck & Co, Inc. Pepcid [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2011.
114. Vial T, Goubier C, Bergeret A, Cabrera F, Evreux JC, Descotes J. Side effects of ranitidine. *Drug Saf*. 1991;6(2):94–117. Epub 1991/03/01
115. Olson JC, Saeian K. Gastrointestinal Issues in Liver Disease. *Crit Care Clin*. 2016;32(3):371–84. Epub 2016/06/25
116. Albani F, Tame MR, De Palma R, Bernardi M. Kinetics of intravenous metoclopramide in patients with hepatic cirrhosis. *Eur J Clin Pharmacol*. 1991;40(4):423–5. Epub 1991/01/01
117. Bernardi M, Trevisani F, Gasbarrini G. Metoclopramide administration in advanced liver disease. *Gastroenterology*. 1986;91(2):523. Epub 1986/08/01
118. Magueur E, Hagege H, Attali P, Singlas E, Etienne JP, Taburet AM. Pharmacokinetics of metoclopramide in patients with liver cirrhosis. *Br J Clin Pharmacol*. 1991;31(2):185–7. Epub 1991/02/01
119. Uribe M, Ballesteros A, Strauss R, Rosales J, Garza J, Villalobos A, et al. Successful administration of metoclopramide for the treatment of nausea in patients with advanced liver disease. A double-blind controlled trial. *Gastroenterology*. 1985;88(3):757–62. Epub 1985/03/01
120. Baxter Healthcare Corporation. Reglan [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2010.
121. GlaxoSmithKline. Zofran [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014.
122. Figg WD, Dukes GE, Pritchard JF, Hermann DJ, Lesesne HR, Carson SW, et al. Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol*. 1996;36(3):206–15. Epub 1996/03/01
123. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160(6):809–15. Epub 2000/03/29
124. Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol*. 2010;8(9):800–5. Epub 2010/06/23
125. Reichert JA, Hlavinka PF, Stolz JC. Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. *Pharmacotherapy*. 2014;34(10):1043–9. Epub 2014/07/24
126. Shatzel J, Dulai PS, Harbin D, Cheung H, Reid TN, Kim J, et al. Safety and efficacy of pharmacological thromboprophylaxis for hospitalized patients with cirrhosis: a single-center retrospective cohort study. *J Thromb Haemost*. 2015;13(7):1245–53. Epub 2015/05/09
127. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e195S–226S. Epub 2012/02/15
128. Al-Dorzi HM, Tamim HM, Aldawood AS, Arabi YM. Venous thromboembolism in critically ill cirrhotic patients: practices of prophylaxis and incidence. *Thrombosis*. 2013;2013:807526. Epub 2014/01/05
129. Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e495S–530S. Epub 2012/02/15
130. Swan SK, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. *Pharmacotherapy*. 2000;20(3):318–29. Epub 2000/03/24
131. Levine RL, Hursting MJ, McCollum D. Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest*. 2006;129(5):1167–75. Epub 2006/05/11
132. Keegan SP, Gallagher EM, Ernst NE, Young EJ, Mueller EW. Effects of critical illness and organ failure on therapeutic argatroban dosage requirements in patients with suspected or confirmed heparin-induced thrombocytopenia. *Ann Pharmacother*. 2009;43(1):19–27. Epub 2009/01/01
133. Saugel B, Phillip V, Moessmer G, Schmid RM, Huber W. Argatroban therapy for heparin-induced thrombocytopenia in ICU patients with multiple organ dysfunction syndrome: a retrospective study. *Crit Care*. 2010;14(3):R90. Epub 2010/05/22
134. Nanchal RS, Ahmad S. Infections in liver disease. *Crit Care Clin*. 2016;32(3):411–24. Epub 2016/06/25
135. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology*. 2010;139(4):1246–56. 56 e1–5. Epub 2010/06/19
136. Fernandez J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology*. 2012;55(5):1551–61. Epub 2011/12/21



137. Fernandez J, Navasa M, Gomez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*. 2002;35(1):140–8. Epub 2002/01/12
138. Merli M, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol*. 2010;8(11):979–85. Epub 2010/07/14
139. Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Casewell M, et al. Fungal infection: a common, unrecognised complication of acute liver failure. *J Hepatol*. 1991;12(1):1–9. Epub 1991/01/01
140. Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Gimson A, et al. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology*. 1990;11(1):49–53. Epub 1990/01/01
141. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL special conference 2013. *J Hepatol*. 2014;60(6):1310–24. Epub 2014/02/18
142. Halilovic J, Heintz BH. Antibiotic dosing in cirrhosis. *Am J Health Syst Pharm*. 2014;71(19):1621–34. Epub 2014/09/17
143. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014;58(8):1072–83. Epub 2014/01/17
144. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Med*. 2013;39(12):2070–82. Epub 2013/09/21
145. Moore RD, Smith CR, Lietman PS. Increased risk of renal dysfunction due to interaction of liver disease and aminoglycosides. *Am J Med*. 1986;80(6):1093–7. Epub 1986/06/01
146. Singh N, Yu VL, Miele LA, Wagener MM. Beta-Lactam antibiotic-induced leukopenia in severe hepatic dysfunction: risk factors and implications for dosing in patients with liver disease. *Am J Med*. 1993;94(3):251–6. Epub 1993/03/01
147. Starr SP, Raines D. Cirrhosis: diagnosis, management, and prevention. *Am Fam Physician*. 2011;84(12):1353–9. Epub 2012/01/11
148. Eshraghian A, Taghavi SA. Systematic review: endocrine abnormalities in patients with liver cirrhosis. *Arch Iran Med*. 2014;17(10):713–21. Epub 2014/10/13
149. Garcia-Compean D, Gonzalez-Gonzalez JA, Lavallo-Gonzalez FJ, Gonzalez-Moreno EI, Maldonado-Garza HJ, Villarreal-Perez JZ. The treatment of diabetes mellitus of patients with chronic liver disease. *Ann Hepatol*. 2015;14(6):780–8. Epub 2015/10/06
150. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009;180(8):821–7. Epub 2009/03/26
151. Chung K, Bang S, Kim Y, Chang H. Intraoperative severe hypoglycemia indicative of post-hepatectomy liver failure. *J Anesth*. 2016;30(1):148–51. Epub 2015/09/04
152. Pfortmueller CA, Wiemann C, Funk GC, Leichtle AB, Fiedler GM, Exadaktylos AK, et al. Hypoglycemia is associated with increased mortality in patients with acute decompensated liver cirrhosis. *J Crit Care*. 2014;29(2):316 e7–12. Epub 2013/12/18
153. American DA. 13. Diabetes care in the hospital. *Diabetes Care*. 2016;39(Suppl 1):S99–104. Epub 2015/12/24
154. Ahmadieh H, Azar ST. Liver disease and diabetes: association, pathophysiology, and management. *Diabetes Res Clin Pract*. 2014;104(1):53–62. Epub 2014/02/04
155. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. *J Gastroenterol Hepatol*. 1995;10(3):344–50. Epub 1995/05/01
156. Silveira MG, Mendes FD, Diehl NN, Enders FT, Lindor KD. Thyroid dysfunction in primary biliary cirrhosis, primary sclerosing cholangitis and non-alcoholic fatty liver disease. *Liver Int*. 2009;29(7):1094–100. Epub 2009/03/18
157. Tas A, Koklu S, Beyazit Y, Kurt M, Sayilir A, Yesil Y, et al. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. *Am J Med Sci*. 2012;344(3):175–9. Epub 2011/12/07
158. Caregaro L, Alberino F, Amodio P, Merkel C, Angeli P, Plebani M, et al. Nutritional and prognostic significance of serum hypothyroxinemia in hospitalized patients with liver cirrhosis. *J Hepatol*. 1998;28(1):115–21. Epub 1998/04/16
159. Fernandez J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44(5):1288–95. Epub 2006/10/24
160. Iihara N, Kurosaki Y, Takada M, Morita S. Risk of hypoglycemia associated with thyroid agents is increased in patients with liver impairment. *Int J Clin Pharmacol Ther*. 2008;46(1):1–13. Epub 2008/01/26
161. Anastasiadis SN, Gioulele OI, Germanidis GS, Vasiliadis TG. Relative adrenal insufficiency in cirrhotic patients. *Clin Med Insights Gastroenterol*. 2015;8:13–7. Epub 2015/03/18
162. Marik PE, Gayowski T, Starzl TE, Hepatic Cortisol R, Adrenal Pathophysiology Study G. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med*. 2005;33(6):1254–9. Epub 2005/06/09
163. Trifan A, Chiriac S, Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. *World J Gastroenterol*. 2013;19(4):445–56. Epub 2013/02/06
164. Fede G, Spadaro L, Tomaselli T, Privitera G, Piro S, Rabuazzo AM, et al. Assessment of adrenocortical reserve in stable patients with cirrhosis. *J Hepatol*. 2011;54(2):243–50. Epub 2010/11/09
165. Thevenot T, Borot S, Remy-Martin A, Sapin R, Cervoni JP, Richou C, et al. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. *Liver Int*. 2011;31(3):425–33. Epub 2011/02/02
166. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med*. 2003;139(3):194–204. Epub 2003/08/06
167. Kazlauskaitė R, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab*. 2008;93(11):4245–53. Epub 2008/08/14
168. Degand T, Monnet E, Durand F, Grandclement E, Ichai P, Borot S, et al. Assessment of adrenal function in patients with acute hepatitis using serum free and total cortisol. *Dig Liver Dis*. 2015;47(9):783–9. Epub 2015/06/17
169. Vincent RP, Etogo-Asse FE, Dew T, Bernal W, Alaghband-Zadeh J, le Roux CW. Serum total cortisol and free cortisol index give different information regarding the hypothalamus-pituitary-adrenal axis reserve in patients with liver impairment. *Ann Clin Biochem*. 2009;46(Pt 6):505–7. Epub 2009/09/04
170. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(2):364–89. Epub 2016/01/14
171. Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ*. 2010;182(18):1971–7. Epub 2010/11/10
172. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int*. 2003;23(2):71–7. Epub 2003/03/26
173. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165–228. Epub 2013/01/31



174. Nolin TD, Aronoff GR, Fissell WH, Jain L, Madabushi R, Reynolds K, et al. Pharmacokinetic assessment in patients receiving continuous RRT: perspectives from the kidney health initiative. *Clin J Am Soc Nephrol*. 2015;10(1):159–64. Epub 2014/09/06
175. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol*. 2016;64(1):69–78. Epub 2015/09/02
176. Karvellas CJ, Subramanian RM. Current evidence for extracorporeal liver support systems in acute liver failure and acute-on-chronic liver failure. *Crit Care Clin*. 2016;32(3):439–51. Epub 2016/06/25
177. Majcher-Peszynska J, Peszynski P, Muller SC, Klammt S, Wacke R, Mitzner S, et al. Drugs in liver disease and during albumin dialysis -MARS. *Zeitschrift fur Gastroenterologie*. 2001;39(Suppl 2):33–5. Epub 2005/10/11
178. Roth GA, Sipos W, Hoferl M, Bohmdorfer M, Schmidt EM, Hetz H, et al. The effect of the molecular adsorbent recirculating system on moxifloxacin and meropenem plasma levels. *Acta Anaesthesiol Scand*. 2013;57(4):461–7. Epub 2012/12/15
179. Personett HA, Larson SL, Frazee EN, Nyberg SL, El-Zoghby ZM. Extracorporeal elimination of piperacillin/tazobactam during molecular adsorbent recirculating system therapy. *Pharmacotherapy*. 2015;35(8):e136–9. Epub 2015/08/21
180. Ruggero MA, Argento AC, Heavner MS, Topal JE. Molecular adsorbent recirculating system (MARS((R))) removal of piperacillin/tazobactam in a patient with acetaminophen-induced acute liver failure. *Transpl Infect Dis*. 2013;15(2):214–8. Epub 2013/01/03
181. Mueller SC, Majcher-Peszynska J, Hickstein H, Francke A, Pertschy A, Schulz M, et al. Pharmacokinetics of piperacillin-tazobactam in anuric intensive care patients during continuous venovenous hemodialysis. *Antimicrob Agents Chemother*. 2002;46(5):1557–60. Epub 2002/04/18
182. Matthew AW. Performance standards for antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute: Wayne, PA; 2014.
183. Personett HA, Larson SL, Frazee EN, Nyberg SL, Leung N, El-Zoghby ZM. Impact of molecular adsorbent recirculating system therapy on tacrolimus elimination: a case report. *Transplant Proc*. 2014;46(7):2440–2. Epub 2014/07/16
184. Wittebole X, Hantson P. Use of the molecular adsorbent recirculating system (MARS) for the management of acute poisoning with or without liver failure. *Clin Toxicol*. 2011;49(9):782–93. Epub 2011/11/15
185. Mousavi S, Levkovich B, Mojtahedzadeh M. A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation. *Daru*. 2011;19(5):312–21. Epub 2011/01/01
186. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH. Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. *Intensive Care Med*. 2007;33(6):1018–24. Epub 2007/04/04
187. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care*. 2012;27(6):741 e9–18. Epub 2012/04/24
188. Shekar K, Roberts JA, Ghassabian S, Mullany DV, Ziegenfuss M, Smith MT, et al. Sedation during extracorporeal membrane oxygenation-why more is less. *Anaesth Intensive Care*. 2012;40(6):1067–9. Epub 2012/12/01
189. Shekar K, Roberts JA, McDonald CI, Fisquet S, Barnett AG, Mullany DV, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. *Crit Care*. 2012;16(5):R194. Epub 2012/10/17
190. Shekar K, Roberts JA, Mullany DV, Corley A, Fisquet S, Bull TN, et al. Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. *Anaesth Intensive Care*. 2012;40(4):648–55. Epub 2012/07/21
191. Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC, et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. *Crit Care*. 2015;19:164. Epub 2015/04/19
192. Shekar K, Fraser JF, Roberts JA. Can optimal drug dosing during ECMO improve outcomes? *Intensive Care Med*. 2013;39(12):2237. Epub 2013/09/17
193. Goncalves-Pereira J, Oliveira B. Antibiotics and extracorporeal circulation—one size does not fit all. *Crit Care*. 2014;18(6):695. Epub 2015/02/13

# Non Transplant Surgical Considerations: Hepatic Surgery and Liver Trauma

18

Thomas Carver, Nikolaos Chatzizacharias,  
and T. Clark Gamblin

## Abstract

Surgery represents one of the main options for the management of liver related conditions, including benign or malignant tumors, biliary abnormalities, and trauma. Liver resections are major operations and carried a significant mortality risk until recently. Within the last 30 years the results have significantly improved, with a post-operative mortality below 3% in specialized centers around the world. At the same time, surgery for liver trauma has become quite rare and the majority of patients are managed non-operatively. When an operation is necessary, most are treated with peri-hepatic packing and a staged operation. While there are significant differences between these two groups with liver disease, the complexity of their treatment results in their admission to the intensive care unit (ICU). Caring for postoperative liver patients or those with liver trauma requires a thorough understanding of each disease process, and almost every intensivist will encounter several of these patients throughout a career.

Before a postoperative patient arrives in the ICU, they have undergone an extensive evaluation to ensure that surgery is the best treatment option. Patient operability, tumor resectability, and adequacy of the future liver remnant are taken into consideration before any procedure is performed. Nonetheless, morbidity is still as high as 30–45%, and major complications occur in around 20%. Patients with hepatic trauma suffer similarly high morbidity and, in severe liver injury, mortality exceeds 40%. However, non-operative management and changes in surgical technique have improved survival. Complications in surgical and trauma patients overlap significantly and include typical surgical complications such as post-operative infections, as well as, organ system failure, electrolyte abnormalities, cardiopulmonary events, and venous thromboembolism. Providers must also be familiar with liver-specific complications such as hemorrhage, bile leak/bilomas, liver abscesses, hepatic necrosis, and post-operative hepatic insufficiency when caring for this high-risk patient population.

The intensive care management of the patient with liver-related surgical disease or hepatic trauma may challenge even the most experienced medical practitioner; and, because of the complex nature of these patients, care should be provided in conjunction with a multidisciplinary team capable of providing the diagnostic, endoscopic, medical, and surgical treatments necessary for the best patient outcomes.

T. Carver, M.D. (✉)  
Division of Trauma and Critical Care Surgery, Medical College  
of Wisconsin, Milwaukee, WI 53226, USA  
e-mail: [tcarver@mcw.edu](mailto:tcarver@mcw.edu)

N. Chatzizacharias, M.D. • T.C. Gamblin, M.D., M.S.  
Division of Surgical Oncology, Medical College of Wisconsin,  
Milwaukee, WI, USA  
e-mail: [nchatzizacha@mcw.edu](mailto:nchatzizacha@mcw.edu); [tcgamblin@mcw.edu](mailto:tcgamblin@mcw.edu)

### Keywords

Liver resection • Hepatectomy • Patient operability • Tumor resectability • Future liver remnant • Liver volumetry • Portal vein embolization • Liver anatomy • Brisbane 2000 terminology of liver resections • Complications • Hyperlactemia • Hypophosphatemia • Post-hepatectomy hemorrhage • Bile leak • Post-hepatectomy liver failure • Hepatic trauma • Liver trauma • Liver injury • Biloma • Bile peritonitis • Non-operative management • Solid organ injury • Operative management • Angioembolization • ERCP • Endoscopic retrograde cholangiopancreatography • Non-operative outcomes • Liver trauma mortality • Liver trauma morbidity • Hepatic trauma mortality • Hepatic trauma morbidity • Hepatic packing • Damage control surgery • Contrast extravasation • Contrast blush • AAST grading system

## Learning Objectives

To familiarize the reader with the main concepts of the management of non-transplant, hepatic surgery patients with specific emphasis on the postoperative aspects of their care. The reader will also gain an understanding of the principles of managing liver trauma, as well as the complications associated with hepatic injury.

## 18.1 Introduction to Hepatic Surgery

Since the first planned liver resection by Carl Langenbuch in 1888, liver surgery has significantly evolved through time [1]. Better understanding of hepatic anatomy and physiology, advances in the fields of anesthesia, and advanced liver transection technologies, have significantly improved outcomes. Even major liver resections are performed with an estimated mortality of less than 3% in specialized centers around the world [2–4]. More recently, minimal invasive techniques, such as laparoscopic and robotic surgery, have advanced to the point that they represent a standard approach for non-complicated cases [5, 6].

Surgery is a primary treatment modality for benign or malignant liver disease. The most common indication for liver resection in the Western world is metastasis, with colorectal cancer being the most common source of liver metastatic disease [7, 8]. Resection also has a role in the management of non-colorectal liver metastases [9], such as neuroendocrine tumors, renal cell carcinoma, ovarian cancer, breast cancer, and melanoma. Surgery is the mainstay for treating primary liver tumors [10–13], such as hepatocellular carcinoma and cholangiocarcinoma. Resection of adjacent liver parenchyma is also indicated in gallbladder cancer [14] and when the liver is directly invaded by tumors of adjacent organs, such as colon, stomach, renal, adrenal and retroperitoneal sarcoma. Resection treats symptomatic benign tumors and cysts (adenoma, hemangioma, focal nodular hyperplasia, cystadenoma), and may be necessary when malignant potential or diagnostic uncertainty is present. Surgical man-

agement remains necessary in some cases of benign biliary strictures, intrahepatic cholelithiasis, and infective conditions of the liver (recurrent pyogenic abscesses, recurrent cholangitis, parasitic cysts), when percutaneous or endoscopic treatments have failed [10]. Finally, surgery has a distinct role in liver trauma and liver transplantation.

Due to the diversity of the indications, as well as of the complexity and physiological importance of the organ, the decision to proceed with a liver resection is not taken lightly. The disease stage and biology, as well as the patient's physiological status should be taken into consideration and an individualized plan should be formed, taking into consideration the role of non-surgical treatment modalities. Therefore, the role of a multidisciplinary team and approach in a specialized tertiary setting is of paramount importance.

### 18.1.1 Preoperative Planning

When a resection is considered three main questions have to be addressed: (1) is the patient's general physiological status appropriate to proceed with the operation, (2) is surgical management oncologically appropriate and is the lesion resectable with appropriate margins, and (3) is the future liver remnant volume sufficient?

#### 18.1.1.1 Patient Operability

Liver resections are major operations with potential life-threatening complications; therefore, one must determine whether or not the patient can withstand the surgical procedure. This is based off the patient's functional status and comorbidities, which can be evaluated during the preoperative evaluation of the patient through a detailed medical history, physical exam and basic pre-operative tests. If necessary, more specific investigations, such as pulmonary function tests or cardiac studies can be performed. In cases of poor performance status or significant comorbidities that preclude surgery, alternative management strategies can be recommended by the multidisciplinary team. The most chal-

**Table 18.1** Child—Pugh score

Scoring			
Parameter	1 point	2 points	3 points
Total Bilirubin (mg/dL)	<2	2–3	>3
Serum Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin Time (s)	<4	4–6	>6
Ascites	None	Mild or controlled with medication	Moderate /severe or refractory
Hepatic Encephalopathy	None	Grade I-II	Grade III-IV
Interpretation			
Points	Class	1-year survival	2-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

lenging patients are those with “borderline” functional status. In these situations, medical and nutritional optimization is invaluable in an attempt to achieve operability while reducing the risk of post-operative complications [15].

Special consideration during the preoperative evaluation should be given to underlying liver dysfunction. A substantial number of patients considered for liver surgery have a liver-related condition or disease (ex. hepatitis, alcohol or non-alcohol related steatohepatitis, autoimmune or metabolic related disease etc.) that precludes optimal organ function. The most challenging patients are those with cirrhosis whether or not they have portal hypertension. Various scoring systems have been proposed for risk stratification in these patients. The two most widely used are the Child-Pugh (Table 18.1) and the Model of End-Stage Liver Disease (MELD) (Table 18.2) scores [16, 17]. The Child-Pugh score was initially designed to predict the outcome of surgical management of portal hypertension in the background of liver cirrhosis. A patient with Child’s A cirrhosis has an estimated 85% 2-year survival. The estimated 2-year survival drops to 57% for a Child’s B and to 35% for a Child’s C patient. The MELD score was initially developed to predict 3-month mortality after transjugular intrahepatic portosystemic shunt (TIPS) procedures in chronic liver disease patients. Subsequently, the MELD score was found to be a useful prognostic tool for patients on the liver transplant list and is now used to prioritize these patients. Even though neither of these scoring systems were designed to predict morbidity or mortality after liver resection, they have been found to be reliable surrogates. Numerous studies have confirmed that Child’s A patients tolerate major surgery, including liver surgery, well. Perioperative risk is higher in Child’s B patients; therefore, surgery should be considered on individual case basis in this group. Child’s C patient’s perioperative mortality can be as high as 50% for minor surgical procedures performed under general anesthesia. Similarly, a MELD score of <9 is generally considered safe for liver surgery.

**Table 18.2** The model for end-stage liver disease (MELD) score)

Scoring	
<i>Original calculation formula:</i>	
MELD = $3.78 \times \ln$ [serum total bilirubin (mg/dL)] + $11.2 \times \ln$ [INR] + $9.57 \times \ln$ [serum Creatinine (mg/dL)] + 6.43	
<i>UNOS modifications:</i>	
1. If patient had dialysis twice within the last 7 days, then the factor used for serum Creatinine should be 4 (instead of 3.78)	
2. Any value <1 is given a value of 1 in order to prevent MELD scores below 0	
Interpretation	
Points	3-month mortality
<9	1.9%
10–19	6%
20–29	19.6%
30–39	52.6%
≥40	71.3%

### 18.1.1.2 Lesion Respectability

If the patient is deemed fit for surgery, then the focus turns toward assessment of the disease. The patient is comprehensively staged and the oncological behavior of the disease and anatomical characteristics of the tumor are considered. Modalities such as contrast enhanced Computer Tomography (ceCT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography-CT (PET-CT) and ultrasound (US) (percutaneous, endoscopic, and intra-operative) may all be used to both stage and determine anatomy [18–25]. Surgical planning depends on the oncologic assessment as the clinical and biological behavior of a tumor varies greatly even within the same type of cancer. Due to the complexity of cancer care, management plans should be developed and individualized within a multidisciplinary team.

An operation should be undertaken only if several criteria are fulfilled: resection with clear histological margins (R0), adequate FLR, intact biliary drainage and vascular inflow/outflow. Small lesions in the periphery of the organ or close to the surface are easily resectable. In situations where the above criteria cannot be met, down-staging of the tumor with preoperative chemotherapy may be considered.



Chemotherapy has been shown to improve resectability in up to 13% [26, 27]. A problem that has arisen from pre-operative chemotherapy is that occasionally tumors become radiologically undetectable after treatment. Studies have shown that the complete radiological response does not always correlate with complete pathological response and about 60–75% of disappearing colorectal liver metastases will recur if left unresected [28–30]. Therefore, the proposed management strategy is resection of these lesions, even in cases of complete radiological response. Placement of radiological markers at the beginning of treatment can facilitate future localization of the lesions [31].

### 18.1.1.3 Future Liver Remnant (FLR)

Post-operative complications and liver function is closely associated with the volume of liver remaining after resection, termed Future Liver Remnant (FLR) [32, 33]. Post-operative liver function depends upon both the volume of the FLR and

the functional status of the remaining liver. This means that larger patients or those with liver disease may require larger FLR to achieve adequate liver function. The functional liver volume can be accurately determined by means of CT volumetry if the remaining liver is normal or only mildly diseased; however, inaccuracies arise in cases of diseased liver, such as in cirrhosis, liver atrophy, biliary obstruction or large space occupying lesions [34]. Since liver volumetry does not always correlate with liver function several alternative tests have been proposed to assess the adequacy of the FLR, including indocyanine green clearance and hepatobiliary scintigraphy [35, 36]. Nonetheless, there are no comparative data to suggest that surgical outcomes are improved with the use of these methods.

In order to account for the aforementioned potential inaccuracies, a validated formula has been introduced, which takes into account not only the size of the FLR as measure by CT volumetry, but also the size of the patient [34].

$$\text{Standardized FLR (sFLR)} = \text{measured FLR} / \text{calculated TLV}.$$

$$\text{Calculated TLV} = -794.41 + 1267.28 \times \text{body surface area (BSA)} (\text{m}^2)$$

If FLR volumes are deemed inadequate, different management options may be considered, such as ablation, staged resection or two staged hepatectomy, and associated liver partition and portal vein ligation (ALPPS). Portal vein embolization (PVE) remains the standard approach, in the vast majority of liver centers, to facilitate resection by increasing the volume of the FLR [37–40]. PVE is most commonly performed percutaneously under radiological guidance and increases FLR volume in 3–4 weeks. Diseased livers, diabetic, or post chemotherapy livers may require longer ( $\geq 5$ –6 weeks). Apart from improving the volume of FLR, the degree of hypertrophy (DH) post-PVE gives prognostic information. Patients with a FLR DH  $\geq 5\%$  are less likely to experience hepatic dysfunction after resection when compared to those with  $\leq 5\%$  growth. Finally, another parameter to be considered is the kinetic growth rate (KGR), which is defined as the DH divided by time in weeks [41]. Patients with a KGR of  $< 2\%$ /week have significantly higher rates of post-hepatectomy hepatic insufficiency and 90-day mortality. In cases where PVE does not result in the desired FLR volume, hepatic vein embolization may facilitate further FLR growth, otherwise surgical resection is precluded [42].

In patients with a healthy underlying liver, major liver surgery can be safely performed with a FLR volume of  $> 20\%$  of TLV [43]. On the contrary, in patients with cirrhosis or significant liver disease a FLR volume of  $> 40\%$  is necessary. In patients who have received preoperative chemotherapy

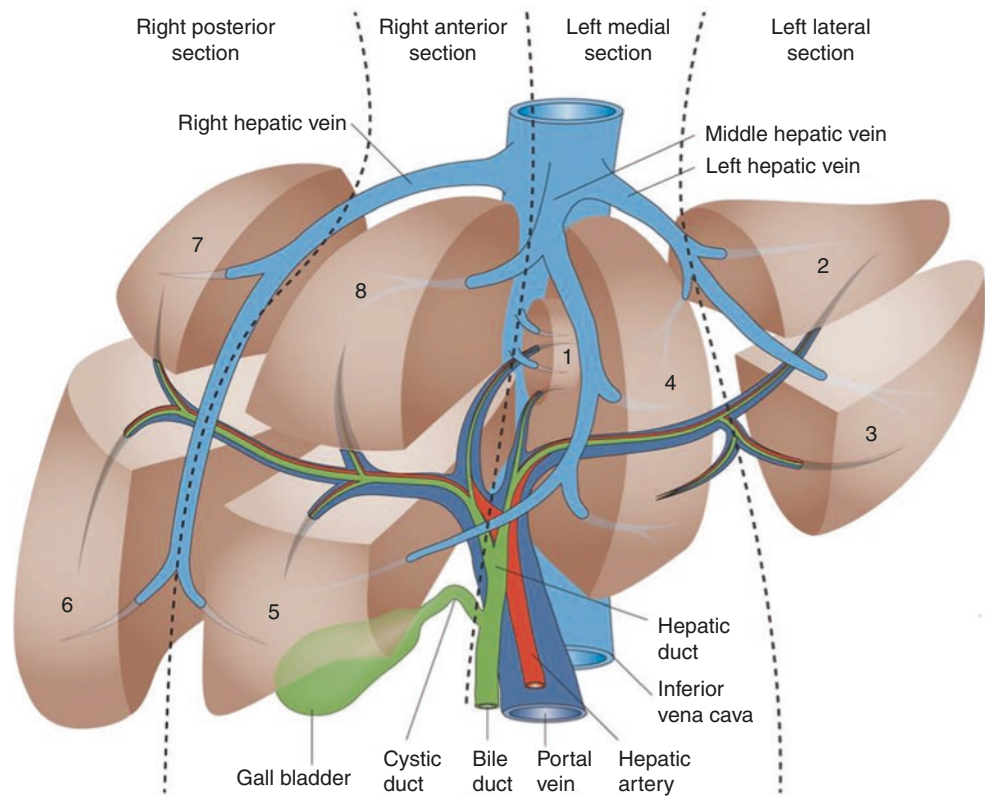
FLR volume of  $> 30\%$  is considered safe. If the status of the FLR is in doubt, a liver biopsy may be performed.

### 18.1.2 Intra-Operative Approach to Liver Surgery

A detailed description of liver anatomy is beyond the purpose of this chapter, however a brief description will facilitate in the understanding of the different types and nomenclature of liver resections. Surgical anatomy of the liver is determined by the intrahepatic vascular and biliary structures. The intrahepatic arterial anatomy can be used to delineate the hepatic lobar, sectional and segmental anatomy [44]. The liver is divided into left and right lobes (generally 40:60 volume ratio) based on the arterial supply of the main hepatic arterial branches. Based on branching of the hepatic artery the liver is divided in sections and segments (Couinaud segments) (Fig. 18.1) [45, 46]. The intrahepatic biliary anatomy generally follows the same pattern as the arterial one. In the right lobe, the portal anatomy and divisions are similar to the hepatic artery, while the left portal vein follows a distinct course corresponding to the embryological function of the vessel. Venous outflow is provided by the three hepatic veins: right, middle and left, which drain into the IVC.

Liver resections can be broadly divided into anatomical (following anatomic planes) and non-anatomical. The terminology used for anatomical liver resections (Brisbane 2000

**Fig. 18.1** Couinaud Hepatic Segmental Anatomy. From [Management of Colorectal Cancer Presenting with Synchronous Liver Metastases](#). Siriwardena AK, et al. *Nat Rev. Clin Oncol.* 2014 Aug;11(8):446–59. Used with permission



Terminology) is based on the intrahepatic arterial anatomy [47]. In general, the surgical goals include elimination of all malignant tissue, hemostasis at the completion of the procedure, avoidance of bile leak, and prevention of FLR injury. Close monitoring and regular clinical assessment are the cornerstones of successful postoperative management.

18.1.3 Postoperative Management of the Liver Surgery Patient

Within the past three decades, results following liver surgery have significantly improved and is performed with a mortality of less than 3% [2–4]. Nonetheless, post-operative morbidity is still high. A recent study on the outcomes of 2313 hepatectomies from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) has shown 2.5% 30-day mortality and 19.6% 30-day major complication rate [48]. Postoperative complications can be divided into those typical after any surgery and those specific for liver surgery. Generic postoperative complications include respiratory and urinary tract infections, surgical wound infections, ileus, organ system failure, cardiopulmonary events, and venous thromboembolism. Liver specific complications occur: significant hemorrhage, bile leak and bilomas, and post-operative hepatic insufficiency. Hepatic insufficiency may lead to fulminant liver failure (Table 18.3).

**Table 18.3** ISGLS definitions and grades of complications after hepatectomy

	Definition	Grades
Hemorrhage	>3 g/dl fall in Hb or need for any post-operative transfusion or intervention for bleeding	A: ≤2 units of PRBC B: > 2 units PRBC C: requiring any intervention
Bile leak	Drain bilirubin level 3 times higher than serum level on or after day 3 or need for any radiological-guided or surgical intervention for bile leak/biloma	A: no need to change routine care plan B: requiring non-surgical intervention C: requiring surgical intervention
Hepatic insufficiency or failure	Impairment of liver synthetic, excretory or detoxifying functions on or after day 5 (elevation in INR or bilirubin)	A: no need to change routine care plan B: requiring special management C: requiring any intervention

*Hb* hemoglobin, *PRBC* packed red blood cells, *INR* international normalized ratio

Furthermore, patients after liver surgery may experience some specific electrolyte abnormalities that would need the attention of the management team. Special care should be considered in the postoperative management of the patient in order to suspect, diagnose and treat any complications early. Due to the potential for these complications patients are fre-

quently admitted to the ICU for postoperative monitoring and the critical care provider must have a thorough understanding of the expected (and unexpected) issues following major hepatectomy.

#### 18.1.4 Electrolyte Abnormalities

Electrolyte abnormalities are common after major hepatectomy especially in cirrhotic patients. Two specific electrolyte abnormalities seen in this population are hyperlactemia and hypophosphatemia. Hyperlactemia is commonly seen following liver resections. High arterial lactate levels in the postoperative period have been correlated with increased morbidity and mortality in these patients [49]. In the postoperative period, due to hepatocellular stress and damage, lactate is produced by the liver, rather than utilized for the purposes of gluconeogenesis, resulting in hyperlactemia [50]. Therefore, in order to avoid the additive effect, the use of non-lactate containing intravenous solutions is recommended [49].

Another electrolyte abnormality that is encountered in almost all patients after major liver surgery is hypophosphatemia. Evidence suggest that it caused by increased urinary loss of phosphate, which is a result of increased levels of the phosphaturic mediators phosphatonins [51, 52]. However, it remains unclear whether the increased phosphatonins levels in post-hepatectomy patients are due to increased production or decreased clearance by the liver. Hypophosphatemia may result in impaired energy metabolism and cellular dysfunction affecting every major organ system. Therefore, careful monitoring of phosphate levels and adequate replacement is required [50].

#### 18.1.5 Postoperative Hemorrhage Recognition and Treatment

The liver receives 25% of the cardiac output and hemorrhage is common both intra- and post-operatively. From NSQIP data, the rate for major intra-operative transfusion (defined as administration of more than 4 units of packed red blood cells (PRBC)) is 9%, while the rate of major post-operative transfusion is 0.8% [53]. On the contrary, different retrospective series have reported an incidence of post-hepatectomy hemorrhage between 1 and 8% [54–56]. The International Study Group on Liver Surgery (ISGLS) defines post-hepatectomy hemorrhage as a fall in the hemoglobin of greater than 3 g/dl after the completion of the operation and/or the need for transfusion and/or intervention (interventional radiology or surgery) for any post-operative hemoglobin drop [57]. The definition is restricted

to the post-operative period and does not include the need for transfusion of up to two units of PRBCs immediately after surgery while in the recovery room. Based on severity, post-hepatectomy hemorrhage has three grades (A–C), which correlate with an increased risk of mortality. Grade A hemorrhage is any episode that requires transfusion of 1 or 2 units of PRBC. Grade B hemorrhage is when more than 2 units of PRBC are transfused. Grade B hemorrhage carries a 17% risk of mortality. Grade C is defined by the need for an intervention to stop the bleeding, either interventional or surgical, and the associated mortality is as high as 50% [57]. For obvious reasons the early diagnosis and appropriate management of post-hepatectomy hemorrhage is paramount.

The diagnosis of bleeding after liver surgery involves the clinical assessment of the patient supplemented by laboratory data and radiologic investigations. Tachycardia, hypotension, oliguria and altered mental status are all signs of hemorrhage but lack specificity in a post-operative patient. Patient factors should be considered as, for example, a patient on beta-blockers may not mount a significant tachycardia in response to hypovolemia while the use of epidural analgesia frequently causes hypotension. Clinical examination may reveal signs of bleeding, however, clinical exam is not reliable because of post-operative pain or pain medications. Serial abdominal exams may detect changes in the clinical picture but are time consuming and still lack sensitivity to diagnose postoperative hemorrhage. Blood within the drain may indicate bleeding, but a misplaced or clogged drain may mislead the bedside clinician. In the absence of hemodynamic instability when diagnosis of hemorrhage is uncertain, radiological imaging is indicated to confirm the diagnosis and guide further management.

The management of the patient consists of resuscitation and hemorrhage control. Resuscitation with crystalloids can be used initially; however, blood products should be employed early if the patient does not respond to fluids or if there is concern for severe hemorrhage. Correction of an underlying coagulopathy should be aggressively corrected in an acutely bleeding patient. Evidence suggests that standard coagulation tests, such as PT, aPTT and INR, do not accurately reflect the postoperative patient's ability to clot [53, 58]. During the first few days after liver surgery thromboelastography (TEG) has demonstrated normal clot formation despite an increased INR. When available, post-operative TEG may provide more accurate evaluation of the patient's coagulation status [58].

Bleeding that does not stop after correction of coagulopathy requires an intervention either in the radiology suite or in the operating room. The method of definitive hemorrhage control depends on the situation and resources available. If a patient is unstable, then returning to the operating room is

usually the safest approach. In certain situations, Interventional Radiology may be utilized for both diagnosis and definitive management.

### 18.1.6 Postoperative Bile Leak and Treatment

Bile leak and biloma formation is another complication specific to liver surgery, with a reported incidence between 3.6 and 12% [59]. ISGLS defines a bile leak as any fluid in the drain with a bilirubin level three times higher than the serum bilirubin level on or after post-operative day three and/or the need for any intervention (image-guided or surgical) for a biloma or biliary peritonitis [59]. Bile leaks also have three grades (A–C), based on the clinical significance. Grade A leaks were defined as those which resolve with conservative management, while grades B and C are those which required an intervention, non-surgical or surgical, respectively. Associated mortality is related to the grade of the bile leak, with reported rates being as high as 39%.

The diagnosis of a bile leak is relatively straightforward when a drain is present. The quality of the fluid in the drain can be clinically assessed and also sent for bilirubin levels. The diagnosis is made when the fluid is bilious or if the fluid bilirubin level is three times higher than the blood bilirubin. If there is no drain in place, a bile leak should be suspected if the patient is failing to improve, has worsening abdominal pain, peritoneal signs, or evidence of an infection. Diagnosis is usually made when a fluid collection is identified and drained (either by CT scan or ultrasound).

The management of bile leaks is based on the principles of adequate drainage and ensuring biliary outflow [60]. If a drain is in place, control is maintained by leaving the drain until the leak resolves. If a surgical drain is not present, drainage can usually be performed percutaneously. Even though some bile leaks resolve with drainage alone, further investigation identify the source of leak and to rule out hepatic biliary obstruction may be necessary. MRCP may answer both of these questions and has the advantage of being non-invasive. If the MRCP is non-diagnostic, or if a stricture or persistent leak (>1 week) is noted, an ERCP should be performed [59]. ERCP can localize the bile leak and also allows for stent placement, which facilitates flow of bile into the duodenum [61]. If ERCP fails (patient intolerance, duodenal diverticulum etc.), the biliary system can be accessed by percutaneous transhepatic cholangiography (PTC) and an antegrade stent placed. Both ERCP and PTC are invasive procedures with inherent morbidity and mortality so they should not be first line management. Thankfully, surgical management of bile leaks after elective liver surgery is rarely required.

### 18.1.7 Hepatic Insufficiency and Failure

Post-operative hepatic insufficiency or failure is the most serious complication after liver resection, with reported rates of up to 19% [60, 62]. Unfortunately, despite best management efforts, post-hepatectomy liver failure related mortality has been reported in up to 90% of the cases [62].

The ISGLS has defined post-hepatectomy hepatic insufficiency as impairment of the liver's synthetic, excretory, or detoxifying functions on or after day five [63], which is determined by serum bilirubin and INR. In patients with normal serum bilirubin and INR pre-operatively, elevated values on or after postoperative day (POD) 5 establishes the diagnosis. In patients with pre-operative hyperbilirubinemia or increased INR levels, the values on POD 5 are compared to those of the previous day. The need for fresh frozen plasma to maintain normal INR on or after POD 5 in combination with hyperbilirubinemia is also diagnostic. Based on a multicenter international study, a bilirubin level >7 mg/dL had sensitivity and specificity higher than 90% and an odds ratio of 10.8 for predicting 90-day mortality [64]. Clinically, hepatic insufficiency varies between minor disturbance in function that requires no special management (grade A), to cases where additional measures are necessary, invasive (grade C) or not (grade B) [63].

The diagnosis of post-hepatectomy liver insufficiency is mainly based on blood biochemistries [63, 64]. In the early post-operative period, a rise in the bilirubin, hepatic enzymes, PT/INR are common and expected. These tend to return to normal levels by POD 7, with the exception of the alkaline phosphatase, which can remain elevated for up to 12 weeks after resection. If these labs do not normalize rapidly, diagnosis of hepatic insufficiency should be considered. Furthermore, low C-reactive protein on POD 1 (<32 g/dL) is an independent predictor of post hepatectomy liver failure [65]. Clinical signs and symptoms, such as jaundice, ascites and, in severe cases, encephalopathy, may be present.

The initial diagnostic approach should include imaging with a contrast CT and/or a liver ultrasound to exclude bile leak and to ensure adequate vascular flow in the FLR. Management is mainly supportive in order to facilitate regeneration. The patient should be transferred to the ICU if not already there. Aggressive supportive care may be necessary as multi-organ system may occur [60]. Broad spectrum antibiotics should be initiated because sepsis is not uncommon in the setting of acute liver failure [60]. Nutritional status should be considered and optimized. Fresh-frozen plasma, vitamin K, albumin, and diuretics may all be required to treat the underlying coagulopathy, hypoalbuminemia, and volume overload, respectively. Liver transplantation may be used as a last resort but is not an option in patients who underwent resection because of a malignancy [60].



## 18.2 Introduction to Hepatic Trauma

Hepatic trauma occurs through either blunt or penetrating mechanisms. While protected by the ribs, the liver's large size makes it particularly vulnerable to penetrating abdominal injuries [66]. In addition, the thin capsule provides little protection from blunt trauma, and the robust vascularity makes hepatic lacerations life threatening [66, 67]. A drastic shift in the management of blunt liver injuries (BLI) has taken place since the 1980's, and, unless they have obvious indications for surgery (i.e., hemodynamic instability or peritoneal signs) almost all patients will have a trial of non-operative management (NOM) [68]. The management of both non-operative and operative hepatic trauma requires close hemodynamic monitoring, and these patients are frequently admitted to the intensive care unit (ICU). This section discusses the fundamentals of the management, outcomes, and complications of hepatic trauma.

### 18.2.1 Background

Liver injury occurs in up to 5% of all traumas and accounts for 25% of intraabdominal injuries [69]. While the rate of penetrating injuries varies depending on loco-regional circumstances, the number of (BLI) has risen over the past several decades [67, 70, 71]. During a 5-year period (1975–1980) 48% of liver injuries were blunt, a number which increased to 74% by the 1990's [70]. While previously a minority of patients, women now account for 46% of all BLI [70]. The widespread use of computerized tomography (CT) in blunt trauma, improved image quality, a higher number of motor vehicle collisions (MVC), and an overall increase in the number of trauma patients [70] are all responsible for the rise in the incidence of BLI [67, 72].

Seventy-five percent of all liver injuries are the result of a MVC [73]. Concomitant injuries are common in patients with hepatic trauma, and up to 55% have associated abdominal injuries [74–76]. The spleen, kidney, and bowel are involved in 21%, 9%, and 4% of liver traumas, respectively [75]. Extra-abdominal injuries also frequently occur, with traumatic brain injury in 14–17%, chest trauma in 46%, and major fractures in 32–72% [66, 77, 78]. Surprisingly, patients with low-grade liver injuries are found to have more splenic (21% vs. 11%) and bowel (30% vs. 10%) injuries when compared to those with high-grade liver trauma [79].

Mortality following liver trauma ranges between 0–60% depending on the grade of injury, and initial management (operative vs. non-operative), and study methodology [80, 81]. A National Trauma Data Bank (NTDB) analysis of over 21,000 patients with liver injury, found an overall mortality of 16.7% which increased with severity of injury (Table 18.4) [80]. A systematic review of 410 patients from all eight prospective

**Table 18.4** Outcomes of all hepatic trauma

Liver injury grade	Patients	Mortality (%)	Non-operatively managed (%)
I and II	14,403	12.7	90.5
III	4099	15.0	78.3
IV	2250	27.9	70.8
V	702	64.8	64.8
VI	78	94.9	62.8
<b>Total</b>	<b>21,532</b>	<b>16.7</b>	<b>85.2</b>

*Adapted from Tinkoff et al.* American Association for the Surgery of Trauma Organ Injury Scale I: Spleen, Liver, and Kidney, Validation Based on the National Trauma Data Bank. *J Am Coll Surg* 2008;207(5):646–55

**Table 18.5** Outcomes of hepatic trauma excluding head injuries

Liver injury grade	Patients	Mortality (%)	Non-operatively managed (%)
I and II	9086	7.0	91
III	2558	9.7	78.5
IV	1310	20.8	72.2
V	379	59.6	61.2
VI	40	92.5	52.5
<b>Total</b>	<b>13,373</b>	<b>10.5</b>	<b>85.9</b>

*Adapted from Tinkoff et al.* American Association for the Surgery of Trauma Organ Injury Scale I: Spleen, Liver, and Kidney, Validation Based on the National Trauma Data Bank. *J Am Coll Surg* 2008;207(5): 646–55

observational studies showed a pooled mortality of only 2.4% in those managed non-operatively [82]. Since most liver injuries are minor (grade 1–3) the mortality from pooled studies may be skewed. When considering only high grade (grade 4–5) BLI, the Consortium of New England Trauma centers found a 21.4% mortality in their non-operative group [74]. The same study showed a 52.7% mortality in patients requiring an immediate operation, but only 5.7% of NOM patients died ( $p < 0.001$ ) [74]. Independent predictors of mortality are older age, ISS, hemodynamic stability, the number of blood transfusions, and presence of a head injury [79, 83]. The impact of associated injuries (especially head injuries) cannot be overstated and there is a substantial decrease in mortality when one considers isolated liver injuries (Table 18.5) [80]. Despite the advances in trauma and critical care over the past century, liver injury still accounts for a significant number of deaths in those with severe abdominal trauma [67].

### 18.2.2 Diagnosis of Hepatic Injury

Historically, liver injuries were diagnosed by laparotomy performed based off physical exam findings or due to a “positive” diagnostic peritoneal lavage (DPL). DPL was overly sensitive and many patients with a liver injury had no procedure performed on their liver [70]. Beginning in the 1980's, as CT

scanning became more available, the number of diagnosed asymptomatic liver injuries increased significantly [70].

Ultrasound has been used extensively in the evaluation of trauma patients and has replaced DPL in the evaluation of unstable patients. Unfortunately, the sensitivity of ultrasound to detect free fluid ranges from 40 to 80% and is even lower if used to detect individual organ injury [84, 85]. Liver function tests (LFTs) have been used as a screening instrument for BLI in pediatrics, and there has been some interest in the use of LFTs in adult patients, as well [86]. LFT abnormalities are associated with grade of liver injury [75]. Although varying levels have been used as cutoffs, a recent paper found that an AST of 109  $\mu\text{L}$  (AUC 0.88) and ALT of 97  $\mu\text{L}$  (AUC 0.88) identified liver injuries [87]. While there has been a call for limiting the amount of radiation that trauma patients are exposed to [88], CT scanning remains the most sensitive and specific modality to diagnose BLI. In any case, almost every trauma patient admitted to the ICU will have had a thorough evaluation which includes a CT scan of the abdomen.

### 18.2.3 Liver Injury Grading System

First devised in 1988, the American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS) provided standardized liver injury nomenclature to providers caring for trauma patients [80]. Severity of liver trauma is graded on a 1–6 scale using the 1994 revision to the OIS (Table 18.6) [89]. Grade 1 injuries are minor while grade 5 represents the most severe injury that is survivable (Fig. 18.2). Grade 1 and 2 hepatic injuries account for 67% of all liver traumas. The remainder are grade 3 (19%), grade 4 (10%), grade 5 (3%), and grade 6 (0.3%) [80]. The OIS has been validated using a large trauma database [80] but significant inter-rater variation exists [90]. Even among experienced trauma surgeons and trauma radiologists, discordance frequently occurs [90]. While providing uniformity for communication, research, and quality improvement initiatives, the OIS grade of liver injury does not predict the need for operative intervention [67, 90, 91]. Regardless of the radiographic finding, patients with liver injuries are either hemodynamically stable or unstable, and that distinction determines further management.

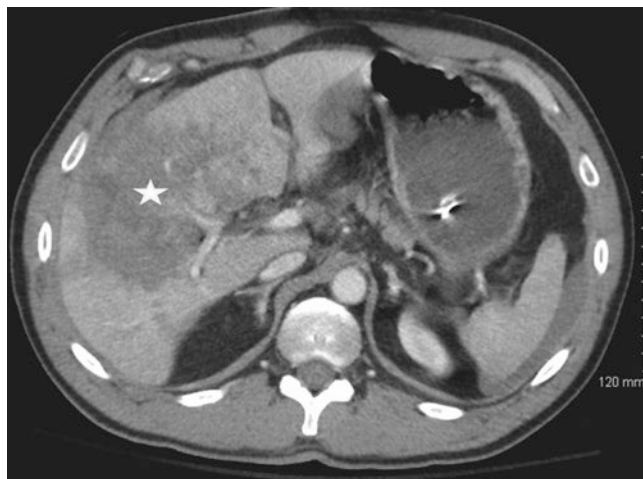
### 18.2.4 Resuscitation of the Patient with Liver Trauma

Initial assessment and treatment of a patient with hepatic trauma follows the principles outlined by the Advanced Trauma Life Support manual (9th edition). As with any other trauma patient, rapid reversal of shock, correction of acidosis, and prevention (or treatment) of hypothermia are

**Table 18.6** AAST liver organ injury scale (1994 revision)

Grade	Injury type	Description of injury
I	Hematoma Laceration	Subcapsular, <10% surface area Capsular tear, <1 cm parenchymal depth
II	Hematoma Laceration	Subcapsular, 10–50% surface area; Intraparenchymal <10 cm in diameter Capsular tear, 1–3 cm parenchymal depth, <10 cm in length
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; Ruptured subcapsular or parenchymal hematoma Intraparenchymal hematoma >10 cm or expanding Capsular tear, <1 cm parenchymal depth
IV	Hematoma Laceration	Ruptured intraparenchymal hematoma with active bleeding Parenchymal disruption involving 25–75% hepatic lobe or 1–3 Couinaud's segments within a single lobe
V	Laceration Vascular	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a single lobe Juxtahepatic venous injury (i.e., retrohepatic vena cava, central major hepatic veins)
VI	Vascular	Hepatic avulsion
Advance one grade for multiple injuries up to grade III		

*Adapted from Moore EE, Shackford SR, Pachter HL, et al.: Organ Injury Scaling: Spleen and Liver (1994 Revision). The Journal of Trauma: Injury, Infection, and Critical Care. 1995;38(3):323–4*



**Fig. 18.2** Grade 5 liver injury. Star identifies the liver laceration involving central venous structures

universal goals. Liver hemorrhage stops spontaneously in the majority of patients [92, 93], and many will not require a blood transfusion. However, there has been a paradigm shift in the past decade toward an earlier use of blood products and a lower reliance on crystalloid fluids during the trauma resuscitation [94–98]. Several terms including balanced, hemostatic, or damage control resuscitation have been used

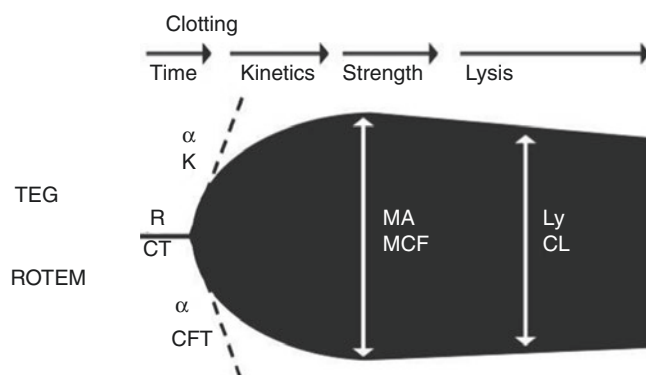
to describe a high plasma ratio transfusion strategy, championed in Borgman et al.'s landmark paper [99]. The reported survival benefit in patients receiving higher ratios of fresh frozen plasma (FFP) to red blood cells (RBC) [100] led trauma centers across the United States to adopt this practice [94, 98, 101]. Massive transfusion protocols (MTP), implemented to provide blood products at higher FFP:RBC ratios, have decreased mortality [97, 101], although their effectiveness has been recently challenged [102]. MTP results in fewer overall transfusions, decreased crystalloid volume, and improved primary fascial closure rates [97, 101, 103]. Optimal transfusion ratios have not been identified and some argue that a 1:1:1 ratio of FFP and platelets to RBC may not be necessary [104]. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial was performed to compare two transfusion ratio strategies (1:1:1 vs. 1:1:2). Although fewer exsanguinations occurred within the 1:1:1 ratio group, the study failed to show a survival difference between the cohorts [105].

More recently, there has been a call for more selective use of blood products, as blind adherence to transfusion ratios may not adequately treat the patient's underlying abnormality [104]. A review of the complex interactions necessary for hemostasis is beyond the scope of this chapter, but it is well known that the traditional tests of coagulopathy (PTT/PT/INR, platelet count, fibrinogen level) all fail to accurately evaluate the hemostatic process [96, 98]. On the other hand, thromboelastography (TEG) or rotational thromboelastometry (ROTEM) both provide graphic representation of clot formation and reliably identify coagulation abnormalities (Fig. 18.3) [95, 104, 106]. The presence of fibrinolysis on TEG has been correlated with an increase in mortality [107, 108]; however, targeted therapy using TEG-guided information has only been shown to improve mortality in one study [109]. TEG-guided resuscitation is correlated with

a reduction in blood product transfusion which may ultimately benefit the patient by decreasing overall costs and limiting exposure to transfusion risks [109].

The Transfusion Requirements in Critical Care (TRICC) trial demonstrated that after resuscitation, trauma patient outcomes were equivalent when a restrictive transfusion strategy was used [110]. Despite this evidence, a survey of members of the American Association for Surgery of Trauma (AAST) showed that ~40% of respondents would transfuse a hemodynamically stable trauma patient whose hemoglobin was >7 g/dl [110]. A restrictive strategy holds particular importance since transfusion within 24 h of admission is an independent risk factor for development of a post-traumatic complication (OR 6.4) [111]. Specific to liver injury is the fact that each unit transfused elevates the risk of complication in a dose-dependent manner, even in those with a lower grade of injury [111]. The results of Sim et al.'s survey show that there is still a significant amount of education necessary regarding the role of transfusion in otherwise stable trauma patients [110].

Despite the risks associated with blood transfusions, an actively bleeding patient should be given blood products and not crystalloid. Damage control resuscitation is a proactive strategy theorized to control hemorrhage with earlier transfusion of FFP and platelets before coagulopathy develops [99]. Although uncertainty surrounding transfusion ratios exists, the treatment of hemorrhaging patients has been fundamentally altered and outcomes have improved. In the 1970's, patients requiring a massive transfusion had a mortality rate of 90%, a figure that now ranges between 30 and 70% [104]. Thankfully, massive crystalloid resuscitation, and the consequences of that strategy such as abdominal compartment syndrome, acute respiratory distress syndrome, open abdomens, and dilutional coagulopathy are rarely seen anymore.



**Fig. 18.3** Thromboelastography: analysis and interpretation of results. R, reaction time/ CT, clotting time. K, kinetics. CFT, clot formation time.  $\alpha$ , alpha-angle. MA, maximum amplitude. MCF, maximum clot firmness. Ly, lysis. CL, clot lysis. Reproduced with permission from Johansson PI et al. Thromboelastography (TEG) in Trauma. *Scand J Trauma Resusc Emerg Med* 2009;17:45

## 18.2.5 Non-Operative Management of Liver Trauma

Non-operative management (NOM) of solid organ injury was first described in patients with splenic trauma in 1892 [112], and was described by Hinton in 1926 [113]. The high mortality associated with the initial experiences of NOM prevented further attempts until reports of splenectomized children developing overwhelming sepsis renewed interest in this treatment strategy [73, 112]. Despite evidence that minor liver injuries were often hemostatic at the time of operation, the prevailing view for decades was that spontaneous cessation of bleeding in severe hepatic trauma was unlikely [91]. Reports from the 1970's confirm this belief as both Ledgerwood and Richardson reported 0% rates of NOM [71]. As surgeons gained experience with splenic NOM, the

use of NOM in liver trauma also expanded [67], becoming common by the 1980's [113]. Croce and colleagues published a prospective study of liver trauma NOM in 1995 and showed that vast majority of patients (89%) could safely avoid an operation [91]. In retrospect, this fact seems obvious but this landmark paper helped show that severe liver injuries (grade 3–5) could be managed non-operatively [91]. An analysis of over 35,000 patients with hepatic trauma showed an increase in NOM from 74.6% to 87.1% between 1994 and 2003, respectively, and demonstrated the quick adoption of NOM within the field of trauma surgery [73]. The advantages of NOM have been reported in multiple studies and include lower hospital costs, reduced length of stay, fewer non-therapeutic laparotomies, fewer transfusions, decreased infections, and lower mortality [68, 76, 114]. Even low volume centers have been shown to successfully perform NOM, with failure rates of 11% [115].

Established criteria for NOM management include hemodynamic stability and lack of other intraabdominal injuries requiring surgery [81, 116]. Initially, altered mental status was considered a contraindication for NOM due to the concern that an unreliable physical exam would result in missed bowel injuries [112]. Archer et al. reviewed their experience in 87 liver trauma patients, 30 (34%) of whom were neurologically impaired. The two cohorts had similar morbidity and mortality. Additionally, no NOM failures occurred in the altered mental status group which provided evidence of the feasibility of NOM even in this subset of patients [112]. A growing body of literature exists regarding NOM of penetrating liver injury [114, 117, 118]. Ten trials have shown a 69–100% rate of NOM success [114]. Selective NOM of penetrating injuries is appropriate using strict criteria within a center that is familiar with the management of liver trauma [117]. Liver related complications are common (50–52%), but NOM demonstrates the potential to decrease non-therapeutic laparotomy rates [114, 117].

While the definition of “stability” is somewhat subjective, the Resuscitation Outcomes Consortium defines shock using the following criteria: systolic blood pressure  $\leq 70$  mm Hg or systolic blood pressure 71–90 mm Hg with heart rate  $\geq 108$  beats per minute [119]. According to the Advanced Trauma Life Support manual an “unstable” patient has a blood pressure  $< 90$  mmHg or a heart rate  $> 120$  bpm, with evidence of skin vasoconstriction or altered mental status [120]. Many “unstable” patients will have improvement in their blood pressure after one or two units of RBCs and should be considered for NOM. Although not validated, several feel that transfusing more than four units of blood due to persistent, liver-related hypotension constitutes failure of NOM [81, 83, 114]. One of the early criticisms of NOM was that this management strategy would lead to an increase in the number of transfusions [121] and, in one study, 45% of patients required a transfusion [83]. Despite this fact, the literature consistently

shows that NOM leads to fewer blood transfusions when compared to the operative strategy [121]. In the presence of combined liver and spleen injuries the total number of transfusions increases significantly, averaging 8.5 units in patients who have successful NOM [121]. While an essential part of liver trauma management, blood transfusions should be limited when physiologically appropriate, especially in light of the dose-related increase in infection and other complications [83].

### 18.2.6 Outcomes of Non-Operative Management

NOM failure rates vary widely in the literature but ranges between 0 and 24%. A study using the NTDB showed that, from 2000 to 2004, NOM was successful in 85.2% of all liver injuries (Table 18.4) [80]. Boese et al.'s systematic review of prospective studies found a NOM failure rate of 9.5% (range 0–24%). This rate is lower than the 20–50% failure rate reported by Carrillo in 1998 [82]. On univariate analysis, only six predictive factors for failure were noted: hypotension on admission, higher volume of crystalloids, need for blood transfusion, peritoneal signs, Injury Severity Score, and other intra-abdominal injuries [82]. Additionally, other intra-abdominal injuries may play a particularly important role in failure of NOM. Velmahos found a 9% NOM failure rate, but none of the operations were performed for liver-specific reasons [71]. Prospective studies show that age, gender, and grade of injury do not correlate with failure of NOM [82].

Since minor liver trauma almost never fails NOM, a separate NTDB study focused on the outcomes of 3627 patients with severe liver injury (AIS  $> 4$ ) [122]. NOM was attempted in 72.5% of these patients with a 93.5% success rate. Van der Wilden et al. found a similarly high (91.5%) NOM success rate in high-grade injuries [74]. Failed NOM was associated with an increased mortality (21.2 vs. 7.1) and an increased LOS (6 vs. 21 days). In another study, significant predictive factors for failure of NOM included age (OR 1.02), male gender (OR 1.73), hypotension (OR 2.07), hepatic artery embolization (HAE) (OR 6.96) and hypotension (8.4% vs. 16%). Again severity of liver injury did not impact success rates [113].

Development of hemodynamic instability is the cause of 75% of NOM failures but only ~50% of failures are due specifically to the liver injury [71, 75, 91, 123]. Polanco et al., noted an increase in failure of NOM in patients with hypotension on arrival [113], leading them to the conclusion that NOM is being offered too liberally. Conversely, Hommes found that hypotension on admission was not related to failure of NOM in severe liver injuries and argues that those who respond to resuscitation can be managed non-operatively [76]. These



diverse factors must be considered in context as the only consistently reliable predictor of failure of NOM is the development of hemodynamic instability, which usually occurs within 48 h of admission [91]. Liver injuries tend to bleed early and, if not, the vast majority of NOM patients will succeed [74].

### 18.2.7 Liver Injury in Cirrhosis

A particularly interesting group of patients are those with underlying liver disease who suffer liver injury. Talving et al. prospectively evaluated 92 cirrhotic patients and compared them to a non-cirrhotic matched cohort [124]. They found a significantly higher complication rate of 31.5% vs. 7.1% and mortality of 20.7% vs. 6.5%. The mortality in those with a Model for End-Stage Liver Disease (MELD) score >10 was 30% vs. 9.5% if the MELD was <10 ( $p = 0.016$ ). Additionally, longer hospital LOS and higher rates of renal failure (5.4 vs. 0.5%) and sepsis (8.7% vs. 2.2%) were also found [124]. Using the NTDB, Barmparas et al. explored the outcomes of cirrhotics following liver injury [125]. NOM was attempted in 83% and failed in 14%, the same failure rate as the control group. Although no significant differences in liver related complications were demonstrated, mortality in the cirrhotic group was 28% vs. 7% in the controls and cirrhotics also required significantly more laparotomies, 58% vs. 17% [125]. While failure of NOM was due to other intraabdominal injuries, the need for trauma laparotomy in a cirrhotic patient is associated with a >50% mortality vs. 4% in the controls [125].

### 18.2.8 Specific Management of NOM Patients

Early in the NOM experience, routine CT scanning was performed, around day 3–7 after injury, and then at intervals throughout the ensuing 12 months until healing was confirmed [91]. Croce showed that the liver injuries had never worsened at the time of the early repeat scan and, in fact, 15% had healed by the time of discharge. When followed long term, the majority of livers had healed by 3–4 months [91]. One study of routine CT scans in liver trauma showed that only three of 503 patients had radiologic findings that mandated treatment. Since these three patients had symptoms related to these findings the authors of that study do not recommend follow-up scans unless clinically indicated [126].

Prolonged bed rest or lengthy ICU admissions are also unnecessary in hepatic trauma unless required by other injuries [114]. The timing of mobilization does not seem to influence failure rates, but no prospective studies exist to support or refute this statement [68]. Since most patients will fail NOM within 24 h, ICU admissions beyond 48 h are probably unnecessary [75, 127]. Following serial hematocrits is also

unnecessary, since as mentioned above, the decision to transfuse blood must be driven by hemodynamic changes and not by a single measured number [127]. In children, the majority of blood transfusions administered after 24 h are done because of anemia and not hemodynamic instability [127]. Using hemodynamic changes to guide the necessity of labs instead of set protocols decreased the number of blood draws from 5 to 1.5 blood draws/patient and had no negative impact on patient outcomes [127].

### 18.2.9 Venous Thromboembolism (VTE) Prophylaxis in Liver Trauma

Few conditions are as synonymous with hypercoagulability as severe trauma. Deep venous thrombosis (DVT) rates exceed 50% in trauma patients not receiving chemical prophylaxis [69, 128]. Even with appropriate prophylaxis, DVT rates are ~15% and the incidence of pulmonary embolism (PE) is 0.13–0.55% [85]. While seemingly insignificant, the mortality after a PE in trauma can be as high as 50% and PE is the third leading cause of death in trauma patients who survive 24 h [69, 85, 129]. Despite this knowledge, the concern for hemorrhage after starting VTE prophylaxis often leads to delayed initiation of prophylaxis [130].

Multiple retrospective studies have assessed the use of DVT prophylaxis in liver trauma [69, 128–131]. Datta et al. published a 4-year retrospective study from Canada of 106 patients with hepatic trauma. While 25% had prophylaxis administered within 48 h, 43% were started >48 h after admission (mean 6 days) and 32% received no prophylaxis at all [69]. Eight (7.5%) DVTs and one (0.9%) PE were diagnosed, all in the delayed group. In a subgroup that included only severe (grades 3–5) liver injuries, no patients receiving prophylaxis within 48 h developed a DVT while 23% in the >48-h group were diagnosed with a DVT. Additionally, no NOM failures were demonstrated in either group despite similar Injury Severity Scores, ICU, or hospital LOS [69]. Eberle et al. showed similar results in a group of patients receiving low molecular weight heparin (LMWH) [128]. Eighteen of 54 (33%) patients started LMWH within three days of injury and the rest were started more than 3 days after injury. Three patients failed NOM, but all of the failures actually occurred before LMWH was administered. Eberle found a 1.3% VTE rate for all solid organ injuries, and only one liver patient developed a DVT [128]. Because no difference was shown in VTE or NOM failure rate the authors concluded that LMWH could safely be used in patients with solid organ injury [128]. Joseph et al. also showed a low VTE rate (1.7%) and no difference in NOM failure rate or in the number of blood transfusions needed after prophylaxis was administered. In fact, only one paper [129] found any significant differences in patient outcomes in patients with solid organ injuries receiving VTE prophylaxis. Despite no significant difference in

NOM failure, VTE rate (1.3%), or in overall need for transfusion, Murphy et al. noted that the group receiving LMWH within 48 h had a higher transfusion rate after starting LMWH when compared to those whose prophylaxis was initiated after 48 h (55% vs. 21%  $p = 0.005$ ) [129].

The paucity of high quality data has prevented the Eastern Association for the Surgery of Trauma from issuing recommendations regarding when to initiate VTE prophylaxis [68] but the American College of Chest Physicians states that prophylaxis should be initiated in most trauma patients within 36 h, provided that there is no evidence of ongoing bleeding [132]. Recent TEG data shows that the hypercoagulability of trauma begins around 48 h after injury [85]. Since no significant differences exist between early and late VTE prophylaxis groups, initiating VTE prophylaxis within 48 h of injury is recommended, provided there are no other contraindications. As noted by Knudson “death from PE is more likely than failure of NOM attributed to prophylactic anticoagulation. If bleeding occurs in this setting, the patient was probably heading for failure anyway [128]”.

### 18.2.10 Operative Management of Liver Injury

Surgery for hepatic trauma has become a rare occurrence, with most surgery residents only performing one operation to control liver hemorrhage during their training [133]. While NOM is standard of care, 13.7% of hepatic traumas will require surgical management [133]. In fact, up to 2/3<sup>rd</sup>s of grade 4–5 livers require laparotomy [114], and the intensive care provider must be familiar with the surgical techniques employed during these operations.

The operative management of liver trauma has undergone extensive evolution over the past 100 years [94]. While packing had been used in the early 1900's, the practice was abandoned because of the significant associated mortality [94]. During World War I, mortality following liver trauma was 66%. With medical and surgical advances, by the 1970's, mortality had improved to as low as 10% [134]. During this time of aggressive surgical management, surgeons used several techniques to control liver hemorrhage including ligation or direct suture control of the vessel, electrocautery, resection, omental packing, and hepatic artery ligation. Unfortunately, these procedures were associated with significant blood loss and mortality [70, 134]. While basically abandoned for decades, in the 1970's case reports of patients surviving after having perihepatic packs placed [134] were published, including a series of four patients who all survived being transferred to a trauma center after liver packing [135]. The resurgence of perihepatic packing as a surgical option came about, in part, because of the realization that coagulopathy was responsible for hepatic trauma deaths [94, 114]. In the 1980's the Denver General group recognized that exsanguinating hemorrhage initiated the

lethal triad (hypothermia, coagulopathy, and acidosis) and recommended the transfusion of platelets and FFP during massive transfusions [94]. A decade later, surgeons reported a large series of patients who were managed with abbreviated surgery, ultimately known as “damage control surgery” (DCS). In this technique, patients undergo an initial operation to control hemorrhage and contamination, and then are transferred to the ICU for correction of their physiologic derangements [94]. Once the acidosis, coagulopathy, and hypothermia are corrected, patients return to the OR for completion of the surgery. Patients with liver trauma usually return to the OR in 48–72 h at which time the packs are removed and definitive hepatic surgery, or repeat packing, performed if necessary. Fortunately, the majority of liver hemorrhages (80%) will stop by simply approximating the parenchyma with packs [136, 137]. When compared with definitive hepatic surgery, perihepatic packing is associated with less blood loss and a significantly lower mortality (34.5% vs. 68%) [70].

In their retrospective analysis of 731 patients with liver trauma over a 14-year period (1999–2013) Suen et al. demonstrated a clear shift toward damage control surgery and increased use of perihepatic packing. In the cohort with high grade injuries (90/731) 31.1% underwent packing, 24.4% local hemorrhage control, 11.1% resection, and 33% had no intervention performed [79]. From 1999 to 2013 damage control laparotomies increased from 6.4% to 23.2% and operative mortality significantly decreased during this period (57.9% to 21.6%) [79].

### 18.2.11 The Impact of Contrast Extravasation, Angiography, and Embolization in Liver Trauma

Advances in CT technology have led to an increased number of patients with identifiable contrast extravasation (blushes) [138, 139] and a grading system has been developed to describe the different patterns of contrast extravasation on enhanced CT scans [139]. In patients with Type 1 extravasation, contrast pools into the peritoneum. Patients with Type 2 extravasation have hemoperitoneum and a blush, but the contrast stays within the liver parenchyma. Patients with Type 3 extravasation have an intraparenchymal blush but no hemoperitoneum [139]. In one study, all patients with a Type 1 blush required an operation to control bleeding within two hours of the CT scan and none of the patients with a Type 3 extravasation required an intervention. Sixty-seven percent of the Type 2 patients became unstable, but the average time to the OR was ~8 h [139]. The sensitivity of contrast pooling to predict need for surgery was 63% [139]. Two other studies have confirmed the finding that intraperitoneal pooling of contrast is associated with the need for surgery, and in both studies, 100% of those patients went on to require a laparotomy [126, 140].

The significance of a contrast blush has been questioned especially since these CT findings may not correlate with angiography. A systematic review of 998 patients who underwent angiography for liver trauma showed that 347 (34.8%) were embolized [72] and retrospective reviews have shown that CT evidence of extravasation predicts an arterial bleed at the time of angiography with a sensitivity of only 56% and a specificity of 83% [141]. Alarheyem et al. reviewed their experience with 788 BLI patients, 72 (9.1%) of whom had a blush on CT scan. Only 67% were found to have extravasation at angiography but the 22 patients without angiographic evidence of ongoing hemorrhage had a significantly higher rate of rebleeding (32% vs. 11%) when compared to the group that was embolized [138]. Based on this finding, the authors recommend empirically performing embolization on patients with a blush on CT scan despite the fact that there were no mortalities in the cohort that rebled [138]. Gaarder et al. implemented a protocol in which all patients with evidence of extravasation on CT underwent angiography, then compared the protocol group to a cohort before routine angiography [142]. Nineteen of 59 patients underwent angiography but only six were found to have active bleeding [142]. The group undergoing angiography as part of a protocol showed a significant reduction in need for laparotomy (34% vs. 58%  $p = 0.009$ ) without impacting NOM failure rates (18 vs. 13%) [142]. Some patients with a contrast blush on CT will benefit from angioembolization; however, given the high percent of negative angiograms reported in the literature, that patient population has not been clearly identified.

Another consideration is the role of angiography in patients who have undergone surgery for hepatic trauma. Several authors have recommended either postoperative angiography [133, 137, 142, 143] or CT scanning [126], citing active arterial bleeding rates of >50% in patients managed with perihaptic packing [133]. Unfortunately, immediate postoperative angiography is only 50% sensitive and 33% specific for finding hepatic bleeding [126]. Postoperative CT scanning that identifies a blush increases the sensitivity and specificity of subsequent angiography to 83% and 75%, respectively [126]. Identifying and treating ongoing hemorrhage with angioembolization may be beneficial. Asensio and colleagues demonstrated a significant mortality reduction in postoperative trauma patients who underwent angioembolization versus those that did not (30% vs. 65%  $p = 0.02$ ) [143].

### 18.2.12 Complications Following Angioembolization

Complications from angioembolization occur in up to 50% of patients in single center studies [93, 137, 144, 145], with hepatic necrosis (14.9%), abscess (6.6%), biloma/bile leak (10.6%), and gallbladder necrosis (4.9%) being the most

common complications [72]. Hepatic necrosis is infrequent because of the dual blood supply of the liver, but when traumatic ischemia is combined with embolization, a large number of hepatocytes can die [72]. Selective embolization results in fewer episodes of hepatic necrosis than when a main branch of the hepatic artery is either ligated or embolized, but if hepatic necrosis does occur, the mortality is ~7% [144]. It is important to note that up to 30% of patients undergoing embolization still require surgery either for bleeding or for another complication [113]. Additionally, even though embolization succeeds 93% of the time (77–100%) delayed bleeding still occurs in 5–12% of patients [72].

### 18.2.13 Complications of Liver Trauma

Complications can be broken into either early or late groups [111]. Within the early group are bleeding and abdominal compartment syndrome (ACS), usually occurring within two days of injury. Biliary and infectious complications, conversely, tend to occur more than three days after injury [111]. As previously noted, morbidity following hepatic trauma is common regardless of operative or non-operative management. With the exception of missed injuries, the risk of complications increases with injury severity, occurring in 1% of grade 3 and in up to 63% of grade 5 injuries (Table 18.7) [68].

Bleeding following NOM of hepatic trauma occurs in only ~8% of severe liver injuries (grade 3–5) but accounts for the majority of hepatic related mortality [111]. This complication can be separated by time from injury (<24 h or >24 h). Of the 35 NOM patients who bled, 20 (57%) were within 24 h. While 15 patients were classified into the “late” bleeding group, all but five of these patients (14%) bled

**Table 18.7** Complications of non-operatively managed liver trauma

Complication	Grade 3	Grade 4	Grade 5	Total (%)
<b>Hemorrhage</b>	<b>6</b>	<b>18</b>	<b>14</b>	<b>38 (43.7)</b>
<24 h	5	9	4	
>24 h	1	8	8	
Rebleeding	0	1	2	
<b>Biliary</b>	<b>6</b>	<b>22</b>	<b>1</b>	<b>29 (33.3)</b>
Biloma	0	11	0	
Bile Leak	2	6	1	
Peritonitis	3	4	0	
Biliary-venous fistula	0	1	0	
Bile duct injury	1	0	0	
<b>Infection</b>	<b>2</b>	<b>11</b>	<b>0</b>	<b>13 (14.9)</b>
Abdominal Sepsis	0	6	0	
Abscess	2	5	0	
<b>Hepatic Necrosis</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>2 (2.3)</b>
<b>ACS</b>	<b>2</b>	<b>1</b>	<b>2</b>	<b>5 (5.8)</b>

Adapted from Kozar et al. Risk Factors for Hepatic Morbidity Following Non-Operative Management. Arch Surg. 2006;141:451–9

within 48 h from injury [111]. Causes of late bleeding include hepatic pseudoaneurysms and hemobilia, which occur in only 1.2% and 3% of hepatic traumas, respectively [114, 117]. Bleeding that occurs more than 72 h after injury is rare and, post-traumatic bleeding (either early or late) can be managed non-operatively ~69% of the time [114].

Abdominal compartment syndrome (ACS), while not unique to hepatic trauma, deserves mention as a complication associated with blunt trauma. ACS develops when elevated intraabdominal pressure occurs as a result of intraperitoneal blood, bowel wall edema, retroperitoneal hematomas, or even packing [116]. Shock (OR 4.51) and blunt trauma (OR 2.38) are the main risk factors and both are commonly seen in patients with severe hepatic trauma [146]. A patient with a firm abdomen who develops difficulty with mechanical ventilation (high peak pressures, hypercapnia, hypoxia), renal failure, or hypotension in the setting of a blunt trauma should have a bladder pressure measured [116]. Development of ACS is associated with a 26% mortality, so any measurement above 25 mmHg should prompt discussion with a surgeon regarding the need for decompressive laparotomy [146].

Biliary complications account for ~1/3rd of all liver-specific complications [81] and manifest by post-injury day 12, on average [111]. The spectrum ranges from small asymptomatic bilomas (a contained collection of bile) to biliary fistulas/leaks and bile peritonitis [81]. When NOM was first being studied HIDA scans were routinely obtained due to the nearly 100% sensitivity/specificity for detecting a bile leak [68]. While ~20% of NOM patients developed bilomas, over 90% of bilomas resolve spontaneously [91]. Bile leaks occur in 4–23% of liver injuries [147] and also usually have a benign course but may require additional treatment. Bile leaks were traditionally diagnosed based on persistent drain output [81] but, in the era of NOM, most bile leaks are diagnosed following image guided drainage of an intraabdominal fluid collection [147]. Leaks are classified into minor (<300 cc/day or >50 cc/day for <2 weeks) or major (>300–400 cc/day or >50 cc for >2 weeks) [147]. The majority of minor bile leaks resolve spontaneously within three weeks as long as adequately drained [81, 114, 147]. Sphincterotomy and stenting are recommended once a major leak is diagnosed because decreasing the pressure gradient may allow for faster leak resolution [81, 148, 149]. In two studies, bile leaks resolved at 6.7 days [148] and 9 days [147] following sphincterotomy and stenting.

Bile peritonitis is another complication following liver trauma and has several overlapping signs that can be confused for sepsis or a missed bowel injury [150]. Bile and blood lead to chemical peritonitis which drives a systemic inflammatory response. Accordingly, patients may develop fevers (>38.5 °C), leukocytosis, tachycardia, abdominal pain, and/or elevated C-reactive protein [151]. When retrospectively evaluated, 5% of patients (10/186) met diagnostic

criteria for “peritoneal inflammatory syndrome,” which developed between 2 and 10 days after injury [151]. Following laparoscopic evacuation of this fluid, a statistically significant decrease in heart rate and maximum temperature were noted [150]. As a result of these findings Franklin, and colleagues have adopted routine, delayed laparoscopic evacuation of fluid collections in patients with high grade liver injuries [150].

On average, hepatic abscesses are not identified until post-injury day 14 [111]. Although rare, intrahepatic abscesses have been associated with a mortality of ~10% in one series [68]. Abscesses and liver necrosis are generally symptomatic and imaging should be obtained in any liver-trauma patient with persistent fever, leukocytosis, or abdominal pain [81, 114]. While the majority of abscesses can be treated with antibiotics and percutaneous drainage, hepatic necrosis is probably best treated with resection as advocated by the group from Shock Trauma [144].

Missed injuries may present in either the early or late period after hepatic trauma. Before NOM management was standard, associated intra-abdominal injuries were noted at laparotomy in 3–13% of patients [78]. Small bowel injuries in patients managed with NOM thankfully occurs in only 1% of patients [71, 111]. Over a three-year period, Miller and colleagues found that 2.3% of their patients had missed injuries, including only two small bowel and three diaphragm injuries [49]. The consequences of missing an injury included a longer length of stay (18 vs. 10 days) and a much higher mortality (43% vs. 5%). These findings emphasize the need to remain vigilant when caring for any patient with liver trauma, especially because all of these missed injuries occurred in patients with low grade liver trauma who were managed non-operatively [49].

Complications following liver trauma are common, occurring in 20–90% of all patients [123, 147], but these complications rarely require any operative intervention [75, 123]. While liver-specific complications were discussed typical ICU-related issues such as pneumonia, bacteremia, multi-organ system failure, etc. also occur with significant frequency, and their effect on mortality cannot be discounted [92, 152]. The fact that patients with severe hepatic injuries survive and develop complications is a testament to the great strides that have been made in the overall care of the traumatized patient.

## Conclusion

The evolution of both hepatic surgery and the management of liver trauma have resulted in dramatically improved outcomes when compared with the shockingly high mortalities noted even within the last 30 years. Complex hepatic resections have become seemingly routine operations in specialized centers and patients considered “unresectable” a few years ago are now being cured through advances in medical and surgical technol-



ogies. Meanwhile, the advances in hepatic trauma have come through a more minimalistic philosophy. The vast majority of blunt liver injury is managed non-operatively and, when a patient requires a laparotomy, the liver is packed in lieu of the complicated hemostatic maneuvers that dominated hepatic trauma surgery for the majority of the past century. Thankfully, when a complication does occur, the variety of endoscopic, endovascular, and percutaneous treatments available have all but eliminated the need for reoperation. In spite of this fact, liver surgery still carries significant risks, and the intensivist should never underestimate the potential for life-threatening bleeding or infection. The complexity of these patients necessitates a team approach between the surgeon and the intensivist to ensure that the patient receives the best care possible.

### 18.3 Hepatic Surgery and Trauma Multiple Choice Questions

1. What is the MELD score that is generally considered safe to perform liver surgery?
  - a. <15
  - b. <12
  - c. <9
  - d. <6

**Answer c.** The MELD score was initially developed to predict 3-month mortality after transjugular intrahepatic portosystemic shunt (TIPS) procedure in chronic liver disease patients. Subsequently, the MELD score was found to be a useful prognostic tool for patients on the liver transplant list and is now used to prioritize these patients. Even though neither of these scoring systems (MELD and Child-Pugh scores) were designed to predict morbidity or mortality after liver resection, in the absence of a better predictor model, they both provide and have been used as reliable substitutes for this purpose. A MELD score of <9 is generally considered safe for liver surgery.

2. Based on current evidence what is the optimal standardized FLR for patients with cirrhosis?
  - a. 20%
  - b. 30%
  - c. 40%
  - d. 50%

**Answer c.** After analysis of surgical outcomes, it is accepted that in patients with a healthy underlying liver, major liver surgery can be safely performed with a sFLR

volume of >20% of TLV [43]. On the contrary, in patients with cirrhosis or significant liver disease a sFLR volume of >40% is necessary. In patients who have received preoperative chemotherapy sFLR volume of >30% is considered safe.

3. What is the level of drain bilirubin that is used to define a biliary leak after hepatic resection based on the ISGLS?
  - a. >3 mg/dl on or after postop day 3.
  - b. 3 times higher than the upper limit of normal on or after postop day 3.
  - c. >3 mg/dl on or after postop day 5.
  - d. 3 times higher than serum bilirubin level on or after postop day 3.

**Answer d.** ISGLS defined bile leak as any fluid in the drain with a bilirubin level 3 times higher than the serum bilirubin level on or after post-operative day 3 and/or the need for any intervention (image-guided or surgical) for a biloma or biliary peritonitis.

4. Which one of the following blood tests may remain high in the post-operative period for even up to 12 weeks?
  - a. Alkaline phosphatase
  - b. ALT (alanine aminotransferase)
  - c. AST (aspartate aminotransferase)
  - d. Bilirubin

**Answer a.** In the early post-operative period, a rise in the bilirubin, hepatic enzymes (ALT and ALP), PT and INR are common and expected [65]. However, these tend to return to normal levels by post-operative day 7, with the exception of the ALP which can remain persistently high for up to 12 weeks post-resection.

5. A patient with hepatitis C cirrhosis underwent a major hepatic resection for hepatocellular carcinoma. The predicted FLR was ~35%. Her INR is elevated to 2 and her bilirubin is 5 mg/dl. Her mental status altered and she is becoming more tachycardic. Regarding hepatic insufficiency following a liver resection which is not true?
  - a. This patient should be transferred to the ICU for monitoring immediately as the mortality associated with liver failure is up to 90%.
  - b. A rapid elevation in ALT and AST are clearly associated with hepatic insufficiency and are used to confirm the diagnosis of liver insufficiency.
  - c. A patient with underlying liver disease will require a larger functional liver remnant when compared to a patient with a normal liver.
  - d. Hepatic ultrasound should be obtained to evaluate the vasculature as either arterial or venous thrombosis can lead to liver insufficiency.

**Answer b.** This patient should be monitored in an ICU setting as they are susceptible to acute decompensation including mental status changes that would require intubation. A larger remnant liver is necessary in patients with underlying liver disease. Hepatic artery thrombosis or portal vein thrombosis both occur following major resection and can lead to liver failure. While ALT and AST can rise acutely following liver surgery the bilirubin and INR are the chemistries used to confirm the diagnosis of postoperative liver insufficiency.

6. Following an automobile crash, a 30-year-old woman is discovered to have a grade 3 liver laceration, a severe pelvis fracture, and a pulmonary contusion. Her hypotension and tachycardia respond transiently to volume replacement. Which of the following statements regarding this patient is true?
- Angioembolization of the liver will result in an improvement in her hypotension.
  - Her hypotension is most likely not related to ongoing liver bleeding.
  - FFP transfusion should be avoided in this patient because of the risk of transfusion reaction.
  - Standard coagulation testing accurately assesses this patient's ability to form clot.

**Answer b.** Only 30% of patients who undergo liver angiogram have embolization performed and, in light of the pelvis fracture, the liver is unlikely to be the source of her shock. FFP should be administered in at least a 1:2 ratio of FFP to RBC. Standard coagulation tests do not accurately assess coagulopathy in either trauma patients or liver surgery patients.

7. A 25-year-old man suffers multiple intraabdominal injuries after a gunshot wound. He had a complex grade 4 liver injury that required packing for hemostasis. His abdomen was closed on postoperative day #2 but he continues to have more than 500 cc of bilious output from his drains on postoperative day #8. The next step in managing this problem is to:
- Continue with conservative management as the bile leak should resolve within 1 week.
  - Consult gastroenterology to perform sphincterotomy and stenting.
  - Have the surgeon return to the operating room to control the bile leak.
  - Obtain an MRCP to define the location of the bile leak.

**Answer b.** while most bile leaks will resolve spontaneously, when a major bile leak is identified sphincterotomy and stenting should be performed as this has been shown to

decrease the duration of the bile leak. Returning to the operating room to control the leak may be necessary but is not the first step in management. An MRCP will confirm a bile leak but does not add prognostic information and is unnecessary in this situation as the drain output is enough to diagnose a bile leak.

8. An 18-year-old man is admitted to the emergency department shortly after being involved in an automobile crash. He is in a coma (Glasgow coma scale score 7). There are closed fractures of the right forearm and the left lower leg. A CT scan of the abdomen revealed a grade 4 liver laceration, a splenic laceration, and a moderate amount of free fluid in the abdomen. All of the following are true EXCEPT:
- The presence of a splenic injury decreases the chance for successful non-operative management of his liver injury.
  - If contrast extravasation is noted on abdominal CT but is contained within the liver, he has a higher risk for needing surgery.
  - He is not a candidate for non-operative management because his head injury limits the ability to detect changes in the abdominal exam.
  - If he requires 6 units of PRBCs within 2 h of arrival because of persistent hypotension, he has failed non-operative management of his liver injury and should be taken to the OR.

**Answer c.** the presence of a head injury does not preclude a trial of non-operative management. Combined intra-abdominal injuries increase the risk for failure of NOM of a liver injury. Contrast extravasation and hemoperitoneum is almost always associated with failure of NOM. Requiring more than 4 units of blood because of hemodynamic instability is a definition of NOM failure.

9. A 17-year-old boy is admitted to the hospital after an automobile crash. His pulse rate is 90 beats per minute and blood pressure 110/70 mmHg. He has minimal abdominal tenderness on exam. An abdominal CT scan reveals a laceration of the left lobe of the liver extending from the dome more than halfway through the parenchyma. Appropriate management includes all of the following EXCEPT:
- 12–24 h of bed rest then progressive amounts of ambulation if he is stable.
  - Abdominal exploration if he develops signs of peritonitis.
  - Checking hemoglobin levels only if the patient's hemodynamics change.
  - Not administering DVT prophylaxis within 48 h in a stable patient because of the liver laceration.

**Answer d.** Although not prospectively studied, there is no evidence that prolonged bed rest >24 h improved NOM rates. Peritonitis is a reason to proceed to the OR. Following hemoglobin levels does not improve outcomes in a patient who is hemodynamically normal. DVT prophylaxis does not increase the risk of NOM failure and should be started within 48 h unless otherwise contraindicated.

10. True statements pertaining to blunt hepatic trauma include which of the following?
  - a. The grade of injury does not predict failure of non-operative management.
  - b. The use of perihepatic packing during surgery is associated with a higher mortality.
  - c. A negative FAST excludes the diagnosis of liver injury.
  - d. The most common complication following NOM of liver injury is hepatic abscess.

**Answer a.** Although several factors are associated with NOM failure, grade of injury is not one of them. Perihepatic packing has led to decreased mortality when compared with definitive liver surgery at the time of initial trauma. FAST lacks the specificity to exclude hepatic injury. Bleeding is the most common early complication of NOM and biliary issues are the most common late complications.

## References

1. Hardy KJ. Liver surgery: the past 2000 years. *Aust N Z J Surg.* 1990;60(10):811–7.
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol.* 2007;25(29):4575–80.
3. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. *Association Francaise de Chirurgie. Cancer.* 1996;77(7):1254–62.
4. House MG, Ito H, Gonen M, Fong YM, Allen PJ, DeMatteo RP, et al. Survival after Hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg.* 2010;210(5):744–52.
5. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg.* 2009;250(5):831–41.
6. Giulianotti PC, Bianco FM, Daskalaki D, Gonzalez-Ciccarelli LF, Kim J, Benedetti E. Robotic liver surgery: technical aspects and review of the literature. *Hepatobiliary Surg Nutr.* 2016;5(4):311–21.
7. Ueno H, Mochizuki H, Hatsuse K, Hase K, Yamamoto T. Indicators for treatment strategies of colorectal liver metastases. *Ann Surg.* 2000;231(1):59–66.
8. Frankel TL, D'Angelica MI. Hepatic resection for colorectal metastases. *J Surg Oncol.* 2014;109(1):2–7.
9. Kulik U, Lehner F, Bektas H, Klempnauer J. Liver resection for non-colorectal liver metastasis—standards and extended indications. *Viszeralmedizin.* 2015;31(6):394–8.
10. Maithel SK, Jarnagin WR, Belghiti J. Hepatic resection for benign disease and for liver and biliary tumors. In: Jarnagin W, Buchler MW, Chapman WC, D'Angelica M, DeMatteo RP, Hann LE, editors. *Blumgart's surgery of the liver, biliary tract and pancreas.* 5th ed. Philadelphia: Elsevier Saunders; 2012. p. 1461–511.
11. Jarnagin W, Chapman WC, Curley S, D'Angelica M, Rosen C, Dixon E, et al. Surgical treatment of hepatocellular carcinoma: expert consensus statement. *HPB (Oxford).* 2010;12(5):302–10.
12. Hartog H, Ijzermans JN, van Gulik TM, Groot KB. Resection of Perihilar Cholangiocarcinoma. *Surg Clin North Am.* 2016;96(2):247–67.
13. Carpizo DR, D'Angelica M. Management and extent of resection for intrahepatic cholangiocarcinoma. *Surg Oncol Clin N Am.* 2009;18(2):289–305. viii–ix
14. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. *J Gastrointest Surg.* 2007;11(5):671–81.
15. Dunne DFJ, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. *Brit J Surg.* 2016;103(5):504–12.
16. Child CG, Turcotte JG. In: Child CG, editor. *Surgery and portal hypertension.* Philadelphia: Saunders; 1964.
17. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001;33(2):464–70.
18. Hagspiel KD, Neidl KF, Eichenberger AC, Weder W, Marincek B. Detection of liver metastases: comparison of superparamagnetic iron oxide-enhanced and unenhanced MR imaging at 1.5 T with dynamic CT, intraoperative US and percutaneous US. *Radiology.* 1995;196(2):471–8.
19. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging.* 2010;31(1):19–31.
20. Sahani D, Mehta A, Blake M, Prasad S, Harris G, Saini S. Preoperative hepatic vascular evaluation with CT and MR angiography: implications for surgery. *Radiographics.* 2004;24(5):1367–80.
21. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology.* 2002;224(3):748–56.
22. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis—meta-analysis. *Radiology.* 2005;237(1):123–31.
23. Ariff B, Lloyd CR, Khan S, Shariff M, Thillainayagam AV, Bansi DS, et al. Imaging of liver cancer. *World J Gastroenterol.* 2009;15(11):1289–300.
24. Baron RL, Brancatelli G. Computed tomographic imaging of hepatocellular carcinoma. *Gastroenterology.* 2004;127(5 Suppl 1):S133–43.
25. Beavers KL, Semelka RC. MRI evaluation of the liver. *Semin Liver Dis.* 2001;21(2):161–77.
26. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg.* 2004;240(4):644–57. discussion 57–8
27. Giacchetti S, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol.* 1999;10(6):663–9.
28. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. *Br J Surg.* 2013;100(11):1414–20.

29. van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J Gastrointest Surg.* 2010;14(11):1691–700.
30. Kuhlmann K, van Hilst J, Fisher S, Poston G. Management of disappearing colorectal liver metastases. *Eur J Surg Oncol.* 2016;42(12):1798–805.
31. Passot G, Odisio BC, Zorzi D, Mahvash A, Gupta S, Wallace MJ, et al. Eradication of missing liver metastases after fiducial placement. *J Gastrointest Surg.* 2016;20(6):1173–8.
32. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN. Total and segmental liver volume variations: implications for liver surgery. *Surgery.* 2004;135(4):404–10.
33. Schindl MJ, Redhead DN, Fearon KCH, Garden OJ, Wigmore SJ. eLISTER. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut.* 2005;54(2):289–96.
34. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg.* 2009;250(4):540–8.
35. Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, et al. Incorporating indocyanin green clearance into the model for end stage liver disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. *Gut.* 2010;59(7):963–8.
36. de Graaf W, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ, et al. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. *J Gastrointest Surg.* 2010;14(2):369–78.
37. Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. *J Am Coll Surg.* 2013;217(1):126–33.
38. Aloia TA. Associating liver partition and portal vein ligation for staged hepatectomy portal vein embolization should remain the gold standard. *JAMA Surg.* 2015;150(10):927–8.
39. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Brit J Surg.* 2007;94(11):1386–94.
40. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg.* 2001;88(2):165–75.
41. Shindoh J, Truty MJ, Aloia TA, Curley SA, Zimmitti G, Huang SY, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg.* 2013;216(2):201–9.
42. Hwang S, Ha TY, Ko GY, Kwon DI, Song GW, Jung DH, et al. Preoperative sequential portal and hepatic vein embolization in patients with hepatobiliary malignancy. *World J Surg.* 2015;39(12):2990–8.
43. Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol.* 2013;20(8):2493–500.
44. Strasberg SM. Hepatic, biliary and pancreatic anatomy. In: Garden OJ, Parks RW, editors. *Hepatobiliary and pancreatic surgery: a companion to specialist surgical practice.* 5th ed. Edinburgh; New York: Elsevier Saunders; 2014. p. 17–30.
45. Couinaud C. Lobes et segments hépatiques: notes sur l'architecture anatomiques et chirurgicales du foie. *Presse Med.* 1954;62:709–12.
46. Siriwardena AK, Mason JM, Mullamitha S, Hancock HC, Jegatheeswaran S. Management of colorectal cancer presenting with synchronous liver metastases. *Nat Rev Clin Oncol.* 2014;11(8):446–59.
47. Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB* 2000; 2:333–39. *HPB (Oxford).* 2002;4(2):99–100.
48. Aloia TA, Fahy BN, Fischer CP, Jones SL, Duchini A, Galati J, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. *HPB (Oxford).* 2009;11(6):510–5.
49. Watanabe I, Mayumi T, Arishima T, Takahashi H, Shikano T, Nakao A, et al. Hyperlactemia can predict the prognosis of liver resection. *Shock.* 2007;28(1):35–8.
50. Wrighton LJ, O'Bosky KR, Namm JP, Senthil M. Postoperative management after hepatic resection. *J Gastrointest Oncol.* 2012;3(1):41–7.
51. Salem RR, Tray K. Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. *Ann Surg.* 2005;241(2):343–8.
52. Datta HK, Malik M, Neely RD. Hepatic surgery-related hypophosphatemia. *Clin Chim Acta.* 2007;380(1–2):13–23.
53. Tzeng CW, Katz MH, Fleming JB, Pisters PW, Lee JE, Abdalla EK, et al. Risk of venous thromboembolism outweighs post-hepatectomy bleeding complications: analysis of 5651 national surgical quality improvement program patients. *HPB (Oxford).* 2012;14(8):506–13.
54. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* 2002;236(4):397–406. discussion -7.
55. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg.* 2000;191(1):38–46.
56. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg.* 2006;243(3):373–9.
57. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ, et al. Post-hepatectomy haemorrhage: a definition and grading by the International study group of liver surgery (ISGLS). *HPB (Oxford).* 2011;13(8):528–35.
58. De Pietri L, Montalti R, Begliomini B, Scaglioni G, Marconi G, Reggiani A, et al. Thromboelastographic changes in liver and pancreatic cancer surgery: hypercoagulability, hypocoagulability or normocoagulability? *Eur J Anaesthesiol.* 2010;27(7):608–16.
59. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery.* 2011;149(5):680–8.
60. Russell MC. Complications following hepatectomy. *Surg Oncol Clin N Am.* 2015;24(1):73–96.
61. Dechene A, Jochum C, Fingas C, Paul A, Heider D, Syn WK, et al. Endoscopic management is the treatment of choice for bile leaks after liver resection. *Gastrointest Endosc.* 2014;80(4):626.
62. Kauffmann R, Fong Y. Post-hepatectomy liver failure. *Hepatobiliary Surg Nutr.* 2014;3(5):238–46.
63. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International study group of liver surgery (ISGLS). *Surgery.* 2011;149(5):713–24.
64. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg.* 2007;204(5):854–62. discussion 62–4.



65. Rahman SH, Evans J, Toogood GJ, Lodge PA, Prasad KR. Prognostic utility of postoperative C-reactive protein for post-hepatectomy liver failure. *Arch Surg.* 2008;143(3):247–53. discussion 53
66. Sawhney C, Kaur M, Gupta B, Singh PM, Gupta A, Kumar S, et al. Critical care issues in solid organ injury: Review and experience in a tertiary trauma center. *Saudi J Anaesth.* 2014;8(Suppl 1):S29–35.
67. Cirocchi R, Trastulli S, Pressi E, Farinella E, Avenia S, Morales Uribe CH, et al. Non-operative management versus operative management in high-grade blunt hepatic injury. *Cochrane Database Syst Rev.* 2015;8:CD010989.
68. Stassen NA, Bhullar I, Cheng JD, Crandall M, Friese R, Guillaumondegui O, et al. Nonoperative management of blunt hepatic injury: an eastern association for the surgery of trauma practice management guideline. *J Trauma Acute Care Surg.* 2012;73(5 Suppl 4):S288–93.
69. Datta I, Ball CG, Rudmik LR, Paton-Gay D, Bhayana D, Salat P, et al. A multicenter review of deep venous thrombosis prophylaxis practice patterns for blunt hepatic trauma. *J Trauma Manag Outcomes.* 2009;3:7.
70. Richardson JD, Franklin GA, Lukan JK, Carrillo EH, Spain DA, Miller FB, et al. Evolution in the management of hepatic trauma: a 25-year perspective. *Ann Surg.* 2000;232(3):324–30.
71. Velmahos GC, Toutouzias KG, Radin R, Chan L, Demetriades D. Nonoperative treatment of blunt injury to solid abdominal organs: a prospective study. *Arch Surg.* 2003;138(8):844–51.
72. Green CS, Bulger EM, Kwan SW. Outcomes and complications of angioembolization for hepatic trauma: a systematic review of the literature. *J Trauma Acute Care Surg.* 2016;80(3):529–37.
73. Hurtuk M, Reed RL 2nd, Esposito TJ, Davis KA, Luchette FA. Trauma surgeons practice what they preach: the NTDB story on solid organ injury management. *J Trauma.* 2006;61(2):243–54. discussion 54–5
74. van der Wilden GM, Velmahos GC, Emhoff T, Brancato S, Georgakis G, Jacobs L, et al. Successful nonoperative management of the most severe blunt liver injuries. a multicenter study of the research consortium of New England centers for trauma. *Arch Surg.* 2012;147(5):423–8.
75. Ward J, Alarcon L, Peitzman AB. Management of blunt liver injury: what is new? *Eur J Trauma Emerg Surg.* 2015;41(3):229–37.
76. Hommes M, Navsaria PH, Schipper IB, Krige JE, Kahn D, Nicol AJ. Management of blunt liver trauma in 134 severely injured patients. *Injury.* 2015;46(5):837–42.
77. She WH, Cheung TT, Dai WC, Tsang SH, Chan AC, Tong DK, et al. Outcome analysis of management of liver trauma: a 10-year experience at a trauma center. *World J Hepatol.* 2016;8(15):644–8.
78. Miller PR, Croce MA, Bee TK, Malhotra AK, Fabian TC. Associated injuries in blunt solid organ trauma: implications for missed injury in nonoperative management. *J Trauma.* 2002;53(2):238–42. discussion 42–4
79. Suen K, Skandarajah AR, Knowles B, Judson R, Thomson BN. Changes in the management of liver trauma leading to reduced mortality: 15-year experience in a major trauma centre. *ANZ J Surg.* 2015;86(11):894–9.
80. Tinkoff G, Esposito TJ, Reed J, Kilgo P, Fildes J, Pasquale M, et al. American association for the surgery of trauma organ injury scale I: spleen, liver, and kidney, validation based on the National trauma data bank. *J Am Coll Surg.* 2008;207(5):646–55.
81. Kozar RA, Moore FA, Moore EE, West M, Cocanour CS, Davis J, et al. Western trauma association critical decisions in trauma: non-operative management of adult blunt hepatic trauma. *J Trauma.* 2009;67(6):1144–8. discussion 8–9
82. Boese CK, Hackl M, Muller LP, Ruchholtz S, Frink M, Lechler P. Nonoperative management of blunt hepatic trauma: a systematic review. *J Trauma Acute Care Surg.* 2015;79(4):654–60.
83. Robinson WP, Ahn J, Stiffler A, Rutherford EJ, Hurd H, Zarzaar BL, et al. Blood transfusion is an independent predictor of increased mortality in nonoperatively managed blunt hepatic and splenic injuries. *J Trauma.* 2005;58(3):437–45.
84. Schnuriger B, Kilz J, Inderbitzin D, Schafer M, Kickuth R, Luginbuhl M, et al. The accuracy of FAST in relation to grade of solid organ injuries: a retrospective analysis of 226 trauma patients with liver or splenic lesion. *BMC Med Imaging.* 2009;9:3.
85. Chapman BC, Moore EE, Barnett C, Stovall RT, Biffl WL, Burlew CC, et al. Hypercoagulability following blunt solid abdominal organ injury: when to initiate anticoagulation. *Am J Surg.* 2013;206(6):917–22. discussion 22–3
86. Ritchie AH, Willisroft DM. Elevated liver enzymes as a predictor of liver injury in stable blunt abdominal trauma patients: case report and systematic review of the literature. *Can J Rural Med.* 2006;11(4):283–7.
87. Koyama T, Hamada H, Nishida M, Naess PA, Gaarder C, Sakamoto T. Defining the optimal cut-off values for liver enzymes in diagnosing blunt liver injury. *BMC Res Notes.* 2016;9:41.
88. Beatty L, Furey E, Daniels C, Berman A, Tallon JM. Radiation exposure from CT scanning in the resuscitative phase of trauma care: a level one trauma centre experience. *CJEM.* 2015;17(6):617–23.
89. Moore EE, Cogbill TH, Jurkovich GJ, Shackford SR, Malangoni MA, Champion HR. Organ injury scaling: spleen and liver (1994 revision). *J Trauma.* 1995;38(3):323–4.
90. Cohn SM, Arango JI, Myers JG, Lopez PP, Jonas RB, Waite LL, et al. Computed tomography grading systems poorly predict the need for intervention after spleen and liver injuries. *Am Surg.* 2009;75(2):133–9.
91. Croce MA, Fabian TC, Menke PG, Waddle-Smith L, Minard G, Kudsk KA, et al. Nonoperative management of blunt hepatic trauma is the treatment of choice for hemodynamically stable patients. *Ann Surg.* 1995;221(6):744–55.
92. Sikhondze WL, Madiba TE, Naidoo NM, Muckart DJ. Predictors of outcome in patients requiring surgery for liver trauma. *Injury.* 2007;38(1):65–70.
93. Bertens KA, Vogt KN, Hernandez-Alejandro R, Gray DK. Non-operative management of blunt hepatic trauma: does angioembolization have a major impact? *Eur J Trauma Emerg Surg.* 2015;41(1):81–6.
94. Roberts DJ, Ball CG, Feliciano DV, Moore EE, Ivatury RR, Lucas CE, et al. History of the innovation of damage control for management of trauma patients: 1902–2016. *Ann Surg.* 2016;265(5):1034–44.
95. Di Saverio S, Sibilio A, Coniglio C, Bianchi E, Biscardi A, Villani S, et al. A proposed algorithm for multimodal liver trauma management from a surgical trauma audit in a western European trauma center. *Minerva Anesthesiol.* 2014;80(11):1205–16.
96. Zentai C, van der Meijden PE, Braunschweig T, Hueck N, Honickel M, Spronk HM, et al. Hemostatic therapy using tranexamic acid and coagulation factor concentrates in a model of traumatic liver injury. *Anesth Analg.* 2016;123(1):38–48.
97. Zaydfudim V, Dutton WD, Feurer ID, Au BK, Pinson CW, Cotton BA. Exsanguination protocol improves survival after major hepatic trauma. *Injury.* 2010;41(1):30–4.
98. Johansson PI, Sorensen AM, Larsen CF, Windelov NA, Stensballe J, Perner A, et al. Low hemorrhage-related mortality in trauma patients in a Level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. *Transfusion.* 2013;53(12):3088–99.
99. Cotton BA, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg.* 2011;254(4):598–605.

100. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. 2007;63(4):805–13.
101. Ball CG, Dente CJ, Shaz B, Wyrzykowski AD, Nicholas JM, Kirkpatrick AW, et al. The impact of a massive transfusion protocol (1:1:1) on major hepatic injuries: does it increase abdominal wall closure rates? *Can J Surg*. 2013;56(5):E128–34.
102. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. *ANZ J Surg*. 2013;83(12):918–23.
103. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma*. 2009;66(1):41–8. discussion 8–9.
104. Tapia NM, Chang A, Norman M, Welsh F, Scott B, Wall MJ Jr, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. *J Trauma Acute Care Surg*. 2013;74(2):378–85. discussion 85–6.
105. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Poddelski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471–82.
106. Johansson PI, Stissing T, Bochen L, Ostrowski SR. Thrombelastography and tromboelastometry in assessing coagulopathy in trauma. *Scand J Trauma Resusc Emerg Med*. 2009;17:45.
107. Ives C, Inaba K, Branco BC, Okoye O, Schochl H, Talving P, et al. Hyperfibrinolysis elicited via thromboelastography predicts mortality in trauma. *J Am Coll Surg*. 2012;215(4):496–502.
108. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2015;19(58):1–228. v-vi.
109. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabian A, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Ann Surg*. 2016;263(6):1051–9.
110. Sim V, Kao LS, Jacobson J, Frangos S, Brundage S, Wilson CT, et al. Can old dogs learn new “transfusion requirements in critical care”: a survey of packed red blood cell transfusion practices among members of the American association for the surgery of trauma. *Am J Surg*. 2015;210(1):45–51.
111. Kozar RA, Moore FA, Cothren CC, Moore EE, Sena M, Bulger EM, et al. Risk factors for hepatic morbidity following nonoperative management: multicenter study. *Arch Surg*. 2006;141(5):451–8. discussion 8–9.
112. Archer LP, Rogers FB, Shackford SR. Selective nonoperative management of liver and spleen injuries in neurologically impaired adult patients. *Arch Surg*. 1996;131(3):309–15.
113. Polanco PM, Brown JB, Puyana JC, Billiar TR, Peitzman AB, Sperry JL. The swinging pendulum: a national perspective of non-operative management in severe blunt liver injury. *J Trauma Acute Care Surg*. 2013;75(4):590–5.
114. Coccolini F, Montori G, Catena F, Di Saverio S, Biffl W, Moore EE, et al. Liver trauma: WSES position paper. *World J Emerg Surg*. 2015;10:39.
115. Norrman G, Tingstedt B, Ekelund M, Andersson R. Non-operative management of blunt liver trauma: feasible and safe also in centres with a low trauma incidence. *HPB (Oxford)*. 2009;11(1):50–6.
116. Chen RJ, Fang JF, Chen MF. Intra-abdominal pressure monitoring as a guideline in the nonoperative management of blunt hepatic trauma. *J Trauma*. 2001;51:44–50.
117. MacGoey P, Navarro A, Beckingham IJ, Cameron IC, Brooks AJ. Selective non-operative management of penetrating liver injuries at a UK tertiary referral centre. *Ann R Coll Surg Engl*. 2014;96(6):423–6.
118. Oyo-Ita A, Chinnock P, Ikpeye IA. Surgical versus non-surgical management of abdominal injury. *Cochrane Database Syst Rev*. 2015;11:CD007383.
119. Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Ann Surg*. 2011;253(3):431–41.
120. ACo S, editor. Advanced trauma life support (ATLS) student course manual. 9th ed. Chicago, IL: American College of Surgeons; 2012.
121. Malhotra AK, Fabian TC, Croce MA, Gavin TJ, Kudsk KA, Minard G, et al. Blunt hepatic injury: a paradigm shift from operative to nonoperative management in the 1990s. *Ann Surg*. 2000;231(6):804–13.
122. Polanco PM, Pinsky MR. Practical issues of hemodynamic monitoring at the bedside. *Surg Clin North Am*. 2006;86(6):1431–56.
123. Velmahos GC, Toutouzas K, Radin R, Chan L, Rhee P, Tillou A, et al. High success with nonoperative management of blunt hepatic trauma: the liver is a sturdy organ. *Arch Surg*. 2003;138(5):475–80.
124. Talving P, Lustenberger T, Okoye OT, Lam L, Smith JA, Inaba K, et al. The impact of liver cirrhosis on outcomes in trauma patients: a prospective study. *J Trauma Acute Care Surg*. 2013;75(4):699–703.
125. Barmparas G, Cooper Z, Ley EJ, Askari R, Salim A. The effect of cirrhosis on the risk for failure of nonoperative management of blunt liver injuries. *Surgery*. 2015;158(6):1676–85.
126. Kutcher ME, Weis JJ, Siada SS, Kaups KL, Kozar RA, Wawrose RA, et al. The role of computed tomographic scan in ongoing triage of operative hepatic trauma: a western trauma association multicenter retrospective study. *J Trauma Acute Care Surg*. 2015;79(6):951–6. discussion 6.
127. Acker SN, Petrun B, Partrick DA, Roosevelt GE, Bensard DD. Lack of utility of repeat monitoring of hemoglobin and hematocrit following blunt solid organ injury in children. *J Trauma Acute Care Surg*. 2015;79(6):991–4. discussion 4.
128. Eberle BM, Schnuriger B, Inaba K, Cestero R, Kobayashi L, Barmparas G, et al. Thromboembolic prophylaxis with low-molecular-weight heparin in patients with blunt solid abdominal organ injuries undergoing nonoperative management: current practice and outcomes. *J Trauma*. 2011;70(1):141–6. discussion 7.
129. Murphy PB, Sothilingam N, Charyk Stewart T, Batey B, Moffat B, Gray DK, et al. Very early initiation of chemical venous thromboembolism prophylaxis after blunt solid organ injury is safe. *Can J Surg*. 2016;59(2):118–22.
130. Joseph B, Pandit V, Harrison C, Lubin D, Kulvatunyou N, Zangbar B, et al. Early thromboembolic prophylaxis in patients with blunt solid abdominal organ injuries undergoing nonoperative management: is it safe? *Am J Surg*. 2015;209(1):194–8.
131. Rostas JW, Manley J, Gonzalez RP, Brevard SB, Ahmed N, Frotnan MA, et al. The safety of low molecular-weight heparin after blunt liver and spleen injuries. *Am J Surg*. 2015;210(1):31–4.
132. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American college of chest physicians evidence-based clinical practice guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):381S–453S.
133. Kozar RA, Feliciano DV, Moore EE, Moore FA, Cocanour CS, West MA, et al. Western trauma association/critical decisions in trauma: operative management of adult blunt hepatic trauma. *J Trauma*. 2011;71(1):1–5.
134. Peitzman AB, Richardson JD. Surgical treatment of injuries to the solid abdominal organs: a 50-year perspective from the Journal of Trauma. *J Trauma*. 2010;69(5):1011–21.

135. Calne RY. The treatment of major liver trauma by primary packing with transfer of the patient for definitive treatment. *Br J Surg*. 1979;66(5):338–9.
136. Di Saverio S, Catena F, Filicori F, Ansaloni L, Coccolini F, Keutgen XM, et al. Predictive factors of morbidity and mortality in grade IV and V liver trauma undergoing perihepatic packing: single institution 14 years experience at European trauma centre. *Injury*. 2012;43(9):1347–54.
137. Letoublon C, Morra I, Chen Y, Monnin V, Voirin D, Arvieux C. Hepatic arterial embolization in the management of blunt hepatic trauma: indications and complications. *J Trauma*. 2011;70(5):1032–6. discussion 6–7
138. Alarhayem AQ, Myers JG, Dent D, Lamus D, Lopera J, Liao L, et al. “Blush at first sight”: significance of computed tomographic and angiographic discrepancy in patients with blunt abdominal trauma. *Am J Surg*. 2015;210(6):1104–10. discussion 10–1
139. Fang JF, Chen RJ, Wong YC, Lin BC, Hsu YB, Kao JL, et al. Classification and treatment of pooling of contrast material on computed tomographic scan of blunt hepatic trauma. *J Trauma*. 2002;49(6):1083–8.
140. Fang JF, Wong YC, Lin BC, Hsu YP, Chen MF. The CT risk factors for the need of operative treatment in initially hemodynamically stable patients after blunt hepatic trauma. *J Trauma*. 2006;61(3):547–53. discussion 53–4
141. Poletti PA, Mirvis SE, Shanmuganathan K, Killeen KL, Coldwell D. CT criteria for management of blunt liver trauma: correlation with angiographic and surgical findings. *Radiology*. 2000;216(2):418–27.
142. Gaarder C, Naess PA, Eken T, Skaga NO, Pillgram-Larsen J, Klow NE, et al. Liver injuries—improved results with a formal protocol including angiography. *Injury*. 2007;38(9):1075–83.
143. Asensio JA, Roldan G, Petrone P, Rojo E, Tillou A, Kuncir E, et al. Operative management and outcomes in 103 AAST-OIS grades IV and V complex hepatic injuries: trauma surgeons still need to operate, but angioembolization helps. *J Trauma*. 2003;54(4):647–53. discussion 53–4
144. Dabbs DN, Stein DM, Philosophe B, Scalea TM. Treatment of major hepatic necrosis: lobectomy versus serial debridement. *J Trauma*. 2010;69(3):562–7.
145. Monnin V, Sengel C, Thony F, Bricault I, Voirin D, Letoublon C, et al. Place of arterial embolization in severe blunt hepatic trauma: a multidisciplinary approach. *Cardiovasc Intervent Radiol*. 2008;31(5):875–82.
146. Strang SG, Van Imhoff DL, Van Lieshout EM, D'Amours SK, Van Waes OJ. Identifying patients at risk for high-grade intra-abdominal hypertension following trauma laparotomy. *Injury*. 2015;46(5):843–8.
147. Hommes M, Nicol AJ, Navsaria PH, Reinders Folmer E, Edu S, Krige JE. Management of biliary complications in 412 patients with liver injuries. *J Trauma Acute Care Surg*. 2014;77(3):448–51.
148. Lubezky N, Konikoff FM, Rosin D, Carmon E, Kluger Y, Ben-Haim M. Endoscopic sphincterotomy and temporary internal stenting for bile leaks following complex hepatic trauma. *Br J Surg*. 2006;93(1):78–81.
149. Anand RJ, Ferrada PA, Darwin PE, Bochicchio GV, Scalea TM. Endoscopic retrograde cholangiopancreatography is an effective treatment for bile leak after severe liver trauma. *J Trauma*. 2011;71(2):480–5.
150. Franklin GA, Richardson JD, Brown AL, Christmas AB, Miller FB, Harbrecht BG, et al. Prevention of bile peritonitis by laparoscopic evacuation and lavage after nonoperative treatment of liver injuries. *Am Surg*. 2007;73:611–7.
151. Letoublon C, Chen Y, Arvieux C, Voirin D, Morra I, Broux C, et al. Delayed celiotomy or laparoscopy as part of the non-operative management of blunt hepatic trauma. *World J Surg*. 2008;32(6):1189–93.
152. Jung K, Kim Y, Heo Y, Lee JCJ, Youn S, Moon J, et al. Management of severe blunt liver injuries by applying the damage control strategies with packing-oriented surgery: experiences at a single institution in Korea. *Hepatogastroenterology*. 2015;62(138):410–6.

# Anesthetic and Perioperative Considerations in Liver Disease (Non-Transplant)

19

Randolph Steadman and Cinnamon Sullivan

## Abstract

The global prevalence of liver disease continues to increase and is currently the second leading cause of mortality in digestive disease in the U.S. The World Health Organization autopsy data shows that 4.5–9.5% of the general population has cirrhosis and the number of surgeries performed in the U.S. and worldwide is continuing to rise. Given the significant impact of anesthetic technique and intraoperative management on morbidity and mortality in this population, this chapter discusses the preoperative workup and optimization of end-stage liver disease (ESLD) patients. Procedures that are specific to ESLD and those commonly performed in ESLD are highlighted.

## Keywords

End-stage liver disease • Cirrhosis • Liver failure • Portal hypertension • Varices • Ascites • Hepatic encephalopathy • Hepatopulmonary syndrome • Portopulmonary hypertension • Cirrhotic cardiomyopathy • Hepatorenal syndrome • Risk stratification and cirrhosis • Coagulopathy and cirrhosis • Thrombophilia and cirrhosis • Transfusion • Factor concentrates • Viscoelastic testing • Systolic pressure variation • Echocardiography • Anesthesia and cirrhosis • Vasopressors and cirrhosis • Intravascular volume and cirrhosis • TIPS • Cholecystectomy • Portal decompression • Sphincteroplasty • Right heart function • Bubble study • Hernia repair • Esophagoduodenoscopy • ERCP

## Learning Objectives

*After reading this chapter the reader should be able to:*

- Identify and describe the two commonly used risk stratification methods for patients with chronic liver disease (CLD)
- Specify the common pathophysiological derangements seen in end-stage liver disease
- List the contraindications to elective surgery in patients with end-stage liver disease

- Recognize the management strategies for preoperative optimization
- Choose intraoperative monitoring based upon the procedure and severity of liver disease
- Evaluate the indications for red cell, plasma, cryoprecipitate and platelet transfusion
- Distinguish the advantages and disadvantages of concentrates (prothrombin complex concentrate and fibrinogen concentrate) from those of conventional factor replacement products
- Appraise anesthetic options for patients with end-stage liver disease
- List contraindications for transjugular intrahepatic portosystemic shunt
- Recognize the difference in anesthetic management for ESLD patients during endoscopy, cholecystectomy, and hernia repair

R. Steadman, M.D., M.S. (✉)  
Department of Anesthesiology and Perioperative Medicine, UCLA  
Health, Los Angeles, CA 90095, USA  
e-mail: [rsteadman@mednet.ucla.edu](mailto:rsteadman@mednet.ucla.edu)

C. Sullivan, M.D.  
Emory University Hospital, Atlanta, GA, USA  
e-mail: [cinnamon.sullivan@emoryhealthcare.org](mailto:cinnamon.sullivan@emoryhealthcare.org)



## 19.1 Preoperative Evaluation and Optimization

### 19.1.1 Preoperative Risk Stratification

Patients with chronic liver disease (CLD) require frequent surgical interventions. Ascites-induced abdominal distension, coupled with loss of muscle tone due to poor nutrition, lead to umbilical and incisional hernias [1]. Umbilical hernias are four times more common in patients with ascites [2]. Peptic ulcer disease is five-fold more prevalent in CLD, affecting 8–20% of patients [3]. The prevalence of gallstones is as high as 25%, elevated in comparison to the general population [4]. Surgical series of cirrhotic patients include orthopedic, cardiac and vascular procedures in addition to gastrointestinal surgery [5]. In an analysis that compared 22,000 patients with cirrhosis to 2.7 million non-cirrhotic patients undergoing one of four index operations—cholecystectomy, colectomy, abdominal aorta repair and coronary artery revascularization—the adjusted hazard ratio for in-hospital mortality was threefold or more higher [6]. This underscores the significant perioperative risk of CLD, and the importance of preoperative evaluation and risk stratification.

Multiple studies have investigated the risk of surgery in patients with cirrhosis [7–9]. These analyses identified various components of the Child–Turcotte–Pugh score, and the composite score, as important prognostic factors for perioperative mortality. In 1964 Child and Turcotte identified five factors—albumin, bilirubin, ascites, encephalopathy, and nutritional status—as important prognostic factors for patients with cirrhosis. Each factor was categorized according to three levels of severity and combined to generate a composite score of one of three classes of severity (class A, B, or C, with C representing the most severe hepatic dysfunction). In 1972 Pugh replacing nutritional status with PT (Table 19.1). The score was originally designed for CLD patients undergoing portosystemic shunt procedures, but subsequently has been applied to CLD patients undergoing other surgeries. In studies conducted over more than 30 years, the modified Child score performed similarly in predicting postoperative mortality: 10% in Child A, 17–30% in Child B, and 60–80% in Child C [8–10]. The 3-month mortality for hospitalized patients not undergoing surgery was 4% for Child A, 14% for Child B, and 51% for Child C [9].

The Model for Endstage Liver Disease (MELD) score was originally designed to predict mortality for patients undergoing transjugular intrahepatic portocaval shunt (TIPS) procedures [11]. Subsequently it was shown to be an improvement to the Child score for the allocation of liver grafts because of its ability to predict 90-day wait list mortality in liver transplant candidates [12]. It replaces the subjective elements of the Child score (ascites, encephalopathy)

**Table 19.1** Modified Child–Pugh Score

	Points <sup>a</sup>		
Presentation	1	2	3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4–6	>6
International normalized ratio	<1.7	1.7–2.3	>2.3
Bilirubin (mg/dL) <sup>b</sup>	<2	2–3	>3
Ascites	Absent	Slight–moderate	Tense
Encephalopathy	None	Grade I–II	Grade III–IV

<sup>a</sup>Class A = 5–6 points; B = 7–9 points; C = 10–15 points

<sup>b</sup>Cholestatic diseases (e.g., primary biliary cirrhosis) produce bilirubin elevations that are disproportionate to the hepatic dysfunction. Thus, the following adjustments should be made: Assign 1 point for a bilirubin level of 4 mg/dL; 2 points for bilirubin concentrations between 4 and 10 mg/dL; and 3 points for bilirubin >10 mg/dL

Kamath PS. Clinical approach to the patient with abnormal liver test results. *Mayo Clin Proc.* 1996;71:1089

with more objective ones, INR and creatinine. The MELD score weighs the continuous variables linearly or logarithmically instead of assigning arbitrary categories, as is the case with the Child score:  $\text{MELD score} = 9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.43$ . In January 2016, serum sodium was added to the MELD score to account for the impact of hyponatremia on waitlist mortality, particularly at lower MELD scores [13]. The resulting formula is:  $\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})]$  [14]. Online calculators are convenient and commonly used to ascertain the MELD score. [<https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/>].

The MELD score has been evaluated as a predictor of perioperative mortality of cirrhotic patients. In a single-center study of 140 surgical procedures, the *c*-statistic for the MELD score's ability to predict 30-day mortality was 0.72. In the cohort of patients undergoing abdominal surgery, the *c*-statistic improved to 0.80. In this study a MELD score between 25 and 30 was associated with a 30-day mortality of 50% after abdominal surgery [15]. Each point in the MELD, up to a score of 20, was associated with to an additional 1% mortality; each MELD point over 20 was associated with an additional 2% mortality. A study of 772 cirrhotics found similar results; a MELD score of 25 was associated with 30-day mortality of 50%. Other predictors of perioperative mortality were age (age >70 equated to 3 MELD points) and coexisting disease (ASA physical status > IV equated to 5 MELD points) [5]. Perioperative complications included liver failure, bleeding, infection, and renal failure. In interpreting their results, these authors concluded that patients with a MELD score of less than 11 have a low postoperative mortality and represent an acceptable risk for elective sur-

gery. In patients with a MELD score of 20 or higher, the high mortality risk contraindicates elective procedures until after liver transplantation. For MELD scores between 11 and 20, the authors recommend surgery at institutions with a liver transplant center so that the transplant evaluation can be undertaken prior to elective surgery [5].

In a retrospective study of 733 cirrhotic patients mortality was associated with a number of factors in addition to the Child score: male gender, the presence of ascites, cryptogenic cirrhosis (vs. other etiologies), elevated creatinine, preoperative infection, higher ASA physical status, and surgery on the respiratory system [16]. The presence of each additional factor conferred additional risk. For instance, 1-year mortality in patients with 6 risk factors was over 80%; mortality with 2 risk factors was approximately 30%.

In patients who present for surgery with elevated liver enzymes, jaundice or unexpected elevation of the prothrombin time, but without a pre-existing diagnosis of liver disease, the etiology of hepatic dysfunction should be determined. Based on case series from the 1960s and 1970s, acute hepatitis confers a prohibitive risk for elective surgery. In a series of 36 patients with undiagnosed hepatitis who underwent laparotomy nearly one-third died. All patients with acute viral or alcoholic hepatitis died. Complications included bacterial peritonitis, wound dehiscence, and hepatic failure [17].

With modern diagnostic testing (serologic testing for hepatitis C, ultrasound testing for gallstones, and improved imaging techniques for hepatic cancer), it is far more likely today that accurate diagnoses can be made preoperatively, avoiding laparotomies in patients with unsuspected hepatitis. In patients diagnosed with acute hepatitis (viral or alcoholic), elective surgery should be postponed until the patient improves clinically and serologically [18, 19]. Acute liver failure (ALF), defined as jaundice, coagulopathy and encephalopathy occurring within a 26 week period in a patient without preexisting liver disease, is a life-threatening condition. Elective surgery should be postponed in this population until after spontaneous recovery or liver transplantation (Steadman 2013) [20].

### 19.1.2 Preoperative Evaluation

The evaluation of hepatic function begins with an inquiry into risk factors and the presence of symptoms attributable to CLD. Prior episodes of jaundice, particularly in relationship to surgical procedures and anesthesia, should be investigated. Alcohol consumption, use of recreational or illicit drugs, medications (including herbal products), presence of tattoos, sexual promiscuity, consumption of raw seafood, and a history of travel to areas in which hepatitis is endemic should be sought. Symptoms of fatigue, anorexia, weight

loss, nausea, vomiting, easy bruising, pruritus, dark-colored urine, biliary colic, abdominal distention, and gastrointestinal bleeding warrant further investigation for the presence of liver disease.

Physical examination findings suggestive of active liver disease include icterus, palmar erythema, spider angiomas, gynecomastia, hepatosplenomegaly, ascites, testicular atrophy, petechiae, ecchymoses, and asterixis. In the absence of findings suggestive of liver disease, routine laboratory tests to assess hepatocellular integrity and hepatic synthetic function are not warranted as false-positive results may be more common than true-positive results in asymptomatic patients. In a study of over 7600 surgical patients who underwent routine preoperative screening, liver enzyme tests were abnormal in roughly 1 of 700 (0.1%) asymptomatic patients. Of the 11 patients with elevations, 3 (1 in 2500 or 0.04%) developed jaundice [21]. Because the normal range for laboratory test is defined as the mean plus or minus two standard deviations, 5% of normal patients can be expected to fall outside the normal range, with 2.5% following above the upper limit of normal. As a result, minor elevations of liver-enzyme results—those less than twice the normal range—may be of no clinical importance [22]. In the presence of abnormal results in an asymptomatic patient the safest approach is to repeat the results; and in the absence of elevations greater than twice the upper limits of normal it is reasonable to proceed with surgery.

In patients with more substantial elevations of liver enzymes, causes include alcohol abuse, medications, chronic hepatitis B and C, NASH, autoimmune hepatitis, hemochromatosis, Wilson's disease, and  $\alpha$ -1 antitrypsin deficiency. Nonhepatic causes include celiac sprue and muscle diseases. Medications include selected antibiotics, antiepileptic drugs, lipid lowering agents, nonsteroidal anti-inflammatory agents, and sulfonylureas.

In patients with known liver disease, a thorough review of systems should be undertaken with an emphasis on the symptoms and signs of encephalopathy, dyspnea (hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension), limited exercise tolerance (infection, electrolyte imbalance, portopulmonary hypertension, coronary artery disease, deconditioning), ascites, gastrointestinal bleeding, and changes in urine output. Hospitalizations should be reviewed along with recent changes in functional status or lab values, and any symptoms or signs of infection. Laboratory evaluation should include determinations of hemoglobin, electrolytes for hyponatremia and acidosis, creatinine, prothrombin time/international normalized ratio, platelet count, fibrinogen level and bilirubin. Room air  $\text{SaO}_2$  is an acceptable test to screen for asymptomatic hepatopulmonary syndrome. In patients undergoing extensive surgery or procedures associated with large fluid volume shifts, transthoracic echocardiography is indicated to screen for

altered systolic or diastolic function, and to rule out asymptomatic portopulmonary hypertension.

### 19.1.3 Preoperative Optimization

Medical management designed to prepare cirrhotic patients for surgery should be directed toward treating active infection, optimizing central blood volume and renal status while minimizing ascites, improving encephalopathy and preparing for possible intraoperative transfusion of red cells and procoagulants. In patients undergoing minimally invasive and percutaneous procedures, platelets and cryoprecipitate can be administered to target platelet count and fibrinogen levels above  $50 \times 10^9/L$  and 1.5 g/L respectively [23]. In patients undergoing open procedures, preoperative prophylactic administration of plasma, cryoprecipitate and platelets are rarely indicated in the absence of active bleeding. Platelets, if indicated, are best administered in the operating room as circulating levels of platelets respond only transiently because of sequestration in the spleen in CLD patients with portal hypertension. Viscoelastic tests such as thromboelastography and thromboelastometry reflect the overall effects of simultaneously decreased levels of endogenous pro- and anticoagulant (protein S, protein C and antithrombin III) factors. If available, viscoelastic testing may be a useful guide for coagulation management [24]. The clinical significance of an abnormal prothrombin time as a predictor of bleeding risk has been questioned because this test reflects only procoagulant factor levels rather than the re-balanced hemostatic system, which may be capable of normal thrombin generation [25]. See the intraoperative management section below for more on coagulation management.

There is little evidence to support specific goal-directed targets for laboratory values or other aspects of preoperative care. The perioperative risk depends more on the operative site and the degree of liver impairment than the anesthetic technique. Upper abdominal surgery (cholecystectomy), when compared to hysterectomy, was associated with liver-enzyme abnormalities, while the anesthetic technique (halothane, enflurane, or fentanyl) was not [26].

In addition to preoperative medical management, efforts should be made to minimize surgical risk through the consideration of less invasive surgery. Laparoscopic cholecystectomy has been shown to be safe in patients with Child–Pugh A and B cirrhosis. In retrospective studies the advantages included low mortality and shorter hospital stay [27, 28]. Child's C patients may benefit from percutaneous drainage of the gallbladder rather than a laparoscopic approach [28]. In a Taiwanese series of over 4000 laparoscopic cholecystectomies, the group with cirrhosis

( $n = 226$ ) had a mortality of approximately 1:100, while mortality was 1:2000 for those without cirrhosis [29]. Meta-analyses of randomized trials in cirrhotic patients showed the laparoscopic approach to cholecystectomy was associated with less blood loss, shorter operative time, and shorter hospitalization compared to an open approach [30, 31]. Preoperative decompression of portal hypertension by TIPS may improve outcomes in patients with severe portal hypertension [32]. However, TIPS is associated with increases in pulmonary artery pressure and can worsen encephalopathy [33, 34].

## 19.2 Intraoperative Management

### 19.2.1 Choice of Monitors

In addition to standard noninvasive monitors, arterial pressure monitoring should be considered for patients with liver disease. The decision is based on the presence of preoperative hypotension, the severity of liver disease, patient age, coexisting diseases of other organ systems, the type and duration of surgery, anticipated intraoperative blood loss, and the need for intraoperative laboratory studies. In patients undergoing liver resection or surgery in the area of the porta hepatis, mobilization of the liver can obstruct the vena cava. Arterial pressure monitoring is very useful under these circumstances.

The usefulness of CVP monitoring is controversial [35]. Many have abandoned CVP monitoring in the setting of liver resection [36]. In our practice, we do not place a central venous catheter exclusively for pressure monitoring. Pulmonary artery catheterization (PAC) is used for patients with known or suspected pulmonary artery hypertension and/or low cardiac ejection fraction. Transesophageal echocardiography (TEE) is the definitive monitor for the assessment of preload, contractility (including regional wall motion), ejection fraction, static and dynamic valvular abnormalities, emboli and pericardial fluid. TEE use may obviate the need for PAC; however, PAC is a better choice for post-operative monitoring, and intraoperatively provides continuous, rather than intermittent, assessment of preload. Preload assessment via TEE is performed using short axis, intragastric views, which may not be technically feasible during mobilization of the liver. Despite these caveats, TEE is a valuable, sensitive intraoperative monitor. In a small series of patients with esophageal varices, TEE universally aided in diagnosis and was not associated with bleeding complications, although transgastric views were avoided to minimize esophageal manipulation [37]. Other authors have confirmed the safety of TEE in this population [38, 39].

### 19.2.2 Coagulation Management

As noted above, viscoelastic testing may be a useful guide for coagulation management because of its ability to reflect the overall balance of clotting and clot lysis. Coagulopathy due to vitamin K deficiency can be corrected by intravenous vitamin K. Some recommend correction of thrombocytopenia ( $<50 \times 10^9/L$ ) prior to minimally invasive procedures [23], while others distinguish between moderate and high risk surgery, recommending platelet counts of  $100 \times 10^9/L$  prior to high risk surgery [40]. Recent data emphasize the central role of fibrinogen in clot stabilization [41]. This has resulted in recommendations to maintain fibrinogen levels above 1.5–2.0 g/L in the presence of hemorrhage [42, 43]. A guideline published in 2016 that focused on the management of critically ill patients with cirrhosis recommended maintaining levels of fibrinogen greater than 1.5 g/L in patients during invasive procedures [23]. These levels align with levels of fibrinogen required for optimal clot formation on viscoelastic testing [42].

Prophylactic administration of FFP to correct INR is controversial in the absence of bleeding. The prophylactic transfusion of FFP to correct a prolonged prothrombin time has limited effectiveness [44] and may be counterproductive by potentiating volume overload (transfusion-associated volume overload, TACO) and exacerbating portal hypertension, leading to an increased risk of variceal bleeding and transfusion-related acute lung injury (TRALI) [45]. Nonetheless, in closed cavity surgeries such as craniotomies, preoperative efforts to normalize the INR are common [46].

Abnormalities in platelet number and function are in part compensated for by increased levels of von Willebrand factor (VWF), a platelet adhesive protein, and by decreased levels of ADAMTS13, the VWF cleaving protease. Thrombin generation is preserved with platelet counts exceeding  $50 \times 10^9/L$ , making this value a practical target in the setting of active bleeding [24].

Prothrombin complex concentrates (PCC), originally developed as a source of FIX for hemophilia B, are available as 3-factor (FII, IX, X) and 4-factor (same plus FVII) products. Some formulations contain endogenous anticoagulants (protein C, protein S, protein Z, antithrombin III) with or without heparin to minimize the thrombotic risk [47]. The majority of PCC safety data has been accumulated in patients requiring rapid reversal of warfarin; these patients' underlying bias toward thrombosis clouds the evaluation of the intrinsic thrombotic risk of PCC. Because of the prolonged half-life of FII and X (60 and 30 h, respectively), repeated dosing of PCC is not recommended [47]. More experience is needed with PCC and its various formulations—currently only one 4-factor PCC is available in the U.S.—to fully understand their role and thrombotic risk in the management of CLD patients.

Fibrinogen concentrates (FC), commonly used in Europe, have not been as widely used in the U.S., where cryoprecipitate remains available. Cryoprecipitate is associated with infectious risk, TRALI (transfusion-related acute lung injury) and TACO (transfusion-related circulatory overload), and has a wide variation in fibrinogen concentration. Fibrinogen concentrates minimize these issues. In two studies comparing efficacy, FC appears to be at least as efficacious as cryoprecipitate [48, 49].

A hemoglobin transfusion trigger of 7 g/dL is reasonable in stable patients; however, in unstable patients with significant bleeding, and in patients with coronary or cerebrovascular disease higher levels may be desirable. Erythropoietin to stimulate red cell production is not recommended in the absence of renal disease [23].

### 19.2.3 Effects of Liver Disease on Anesthetic Drugs

Liver disease affects anesthetic drugs by changing metabolic rate, protein binding, and volume of distribution. Patients with liver disease have a decreased rate of metabolism secondary to reduced liver mass and hepatocyte dysfunction. Factors that affect hepatic clearance include blood flow to the liver, the fraction of the drug unbound to plasma proteins, and intrinsic clearance. Drugs with low extraction ratios, less than 0.3, have restrictive hepatic clearance. Clearance of drugs in this class, such as benzodiazepines, are affected by protein binding, the induction or inhibition of hepatic enzymes, age, and hepatic pathology, but clearance is not significantly affected by hepatic blood flow. Drugs with a high extraction ratio (greater than 0.7) undergo extensive first-pass metabolism, which alters their bioavailability after oral administration. Regardless of the route of administration, drugs with high extraction ratios are significantly affected by alteration in hepatic blood flow, which can occur with hemodynamic changes or hepatic inflow clamping during liver resection. High extraction ratio drugs tend to have short elimination half-lives (e.g., propranolol  $t_{1/2} = 3.9$  h). Most induction agents, including ketamine, etomidate, propofol, and thiopental, are highly lipophilic and have high extraction ratios [50]. Benzodiazepines administered to patients with liver disease have a prolonged elimination half-life. Although metabolism of benzodiazepines is reduced in these patients, free drugs may be increased due to less protein binding [51, 52]. Overall, patient with liver disease display an increased sensitivity to sedatives and analgesics. Metabolism of opioids is reduced in patients with liver disease. The elimination of a single IV opioid bolus is less affected than a continuous infusion through redistribution to storage sites. Dosing intervals of opioids should be increased to avoid drug accumulation. Chronic use of meperidine should be avoided because of accumulation of



the metabolite normeperidine, which can lead to seizure and neurotoxicity [53].

The intermediate duration neuromuscular blocking agents vecuronium and rocuronium are metabolized by the liver and exhibit a prolonged duration of action [54, 55]. Despite this, a resistance to the initial dose of neuromuscular blocker typically occurs due to elevated  $\gamma$ -globulin concentrations and an increase in the volume of distribution (due to edema and/or ascites). Atracurium and cisatracurium undergo organ-independent elimination and their durations of action are not affected by liver disease. Succinylcholine metabolism is altered due to reduced plasma cholinesterase activity in patient with liver disease, but the clinical impact is rarely significant.

#### 19.2.4 Vasopressors and Volume Resuscitation

In contrast to sedatives, patients with liver disease exhibit a reduced responsiveness to endogenous vasoconstrictors including angiotensin II, vasopressin, and norepinephrine [56]. Hyporesponsiveness to catecholamines may be controlled by the release of nitric oxide, prostacyclin, and other endothelial-derived factors in response to humoral and mechanical stimuli [57]. Many patients present with hyperdynamic circulation characterized by low systemic vascular resistance, borderline hypotension and elevated cardiac output. Such patients may not tolerate induction or maintenance of anesthesia without vasopressor support. Evidence suggests that patients with severe liver disease are depleted in endogenous vasopressin [58]. In addition to vasopressin, norepinephrine is a good choice to support systemic vascular resistance fluctuations during the perioperative period.

In patients undergoing abdominal surgery, fluids should be restricted, with or without CVP monitoring, in order to lower portal pressures. When volume resuscitation is needed, the fluid and blood products administered are similar in patients with and without liver disease with several notable exceptions. In chronic liver disease, serum albumin function is quantitatively and qualitatively decreased [59]. Albumin may be chosen over crystalloids for perioperative volume expansion due to its ability to sustain oncotic pressure and minimize postoperative edema. Specific indications for albumin include volume expansion after large volume (4–5 L) paracentesis, in the presence of spontaneous bacterial peritonitis to prevent worsening renal impairment, and in conjunction with splanchnic vasoconstrictors for type I hepatorenal syndrome [60–62].

#### 19.2.5 Effect of Anesthetics on the Liver

Anesthetics affect the liver by altering hepatic blood flow and by undergoing metabolism to hepatotoxic byproducts. Drugs with high extraction ratios are significantly affected

by alteration in hepatic blood flow, which can occur with hemodynamic changes or hepatic inflow clamping during liver resection.

All volatile anesthetics decrease hepatic blood flow to a certain degree. Halothane causes the greatest reduction due to cardiovascular depression. Desflurane can decrease hepatic blood flow by 30% at one MAC [63]. Isoflurane and sevoflurane cause very little hepatic blood reduction at one MAC [64]. At higher concentrations, isoflurane reduces hepatic blood flow in a dose-dependent fashion.

Volatile anesthetics undergo metabolism in the liver and produce reactive trifluoroacetylated (TFA) intermediates. These intermediates can bind to hepatic proteins, causing an immunologic reaction leading to liver injury. The amount of TFA production is highly correlated to the extent of oxidative metabolism of the anesthetic (halothane 20%, isoflurane 0.2% and desflurane 0.02%). Sevoflurane metabolism does not produce TFA intermediates [65]. There is little evidence that volatile anesthetics other than halothane cause severe hepatic injury; however, isolated case reports exist. Sevoflurane undergoes metabolism and produces fluoride and hexafluoroisopropanol (HFIP), which are conjugated by the liver and excreted by the kidney. There is no evidence that these metabolites, or compound A, another metabolite produced in a reaction with carbon dioxide absorbents, cause hepatic injury [66]. Nitrous oxide decreases hepatic blood flow mostly by stimulation of the sympathetic nervous system [67]. In addition, nitrous oxide can inhibit methionine synthase even after brief exposure. The clinical significance of these effects is not clear; however, prolonged exposure could lead to vitamin B<sub>12</sub> deficiency [68].

Intravenous anesthetics (propofol, etomidate, opioids and midazolam) do not appear to affect liver function when given as a single bolus for induction. Prolonged administration of propofol can cause propofol infusion syndrome, which is characterized by lactic acidosis, lipidemia, rhabdomyolysis, hyperkalemia, and myocardial failure [69]. Patients with liver disease may be predisposed to propofol infusion syndrome since alterations of lipid metabolism occur in these patients [70]. Patients on prolonged propofol infusions should be monitored for lactic acidosis and hemodynamic changes.

#### 19.2.6 Neuraxial Anesthesia

The effect of neuraxial anesthesia on hepatic blood flow correlates with changes in systemic blood pressure [71], with epidural anesthesia reducing hepatic blood flow [72]. Whether vasopressors improve or worsen hepatic blood flow is the subject of debate [73, 74], so avoidance of high neuraxial block and hypotension seems prudent in patients with significant CLD. Additionally, patients with severe CLD may present with coagulopathy and thrombocytopenia that contraindicates neuraxial block. A recent study evaluat-

ing the effects of major hepatic resection found that viscoelastic testing remained normal post resection despite increases in prothrombin time and decreases in fibrinogen and platelet count [75]. Two of 16 patients in this series had pulmonary embolism despite conventional lab results suggesting coagulopathy. Whether decisions regarding neuraxial anesthesia can be made on the basis of viscoelastic testing, in the face of contradictory conventional testing, seems premature.

In the absence of specific contraindications, regional anesthesia can be performed in patient with liver disease with the potential benefits of improved pain control, reduction of pulmonary, cardiovascular, and thromboembolic complications, and hastening the recovery of gut function after abdominal surgery. Patients with advanced hepatic disease who are not eligible for neuraxial techniques may benefit from peripheral nerve blockade. Transversus abdominal plane (TAP) block has been successfully used for abdominal surgery in patients with liver disease, even though abdominal wall hematoma has been reported [76].

### 19.3 Common Procedures for ESLD Patients

The global burden of chronic liver disease continues to increase and with that comes the increased need for invasive procedures. Beyond the risk stratification of CTP class and MELD, the variation in anesthetic and surgical expertise along with the knowledge of the critical care team contribute to the wide distribution in intra- and postoperative morbidity and mortality. For end-stage liver disease (ESLD) patients with little hepatic reserve and multiple comorbidities a transfer to a liver transplant center should be considered in order to facilitate the transition to an expedited liver transplant evaluation. ESLD patients have an exaggerated response to surgical and anesthetic stress which can cause a rapid decompensation. While most patients with a low MELD (<8) or Child's class A can be routinely managed at any institution, higher MELD, Child's class B and C, and patient's requiring more complex procedures benefit from clinicians with expertise in treating ESLD.

### 19.4 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Certain sequelae of liver disease are directly attributable to portal hypertension. The efficacy of TIPS in the treatment of refractory ascites and secondary prevention of variceal bleeding has been well studied in controlled trials [77]. Uncontrolled studies of varying size show TIPS to be an effective treatment for the indications below as well.

- Refractory acutely bleeding varices
- Budd-Chiari syndrome
- Refractory hepatic hydrothorax
- Portal hypertensive gastropathy
- Hepatorenal syndrome

When not being performed for direct therapeutic purposes, TIPS can also be used to decrease preoperative risk for other procedures, such as hepatic resection, coronary artery bypass graft, etc. A large part of the morbidity and mortality of surgery performed in cirrhotic patients is due to the degree of portal hypertension present. TIPS reduces the risk of bleeding and amount of ascites, thereby lowering Child's class. Lowering a preoperative MELD-Na score or Child's class by decreasing portal hypertension at least one month before the staged procedure decreases the perioperative mortality risk for that planned surgery [1]. TIPS is less invasive than a surgical shunt for portal decompression and can be performed as either a treatment or as a preoperative intervention. It is a percutaneous method for reducing portal hypertension by creating a channel between a hepatic vein and an intrahepatic branch of the portal vein and is successful >90% of the time [77]. Even with the complexity of severe liver disease major complications after TIPS occurs in less than 5% of patients [78]. Bypassing the fibrotic parenchyma of a cirrhotic liver and creating direct flow from the portal to systemic venous system both alleviates some problems and causes others. Therefore a systematic workup is required and includes a risk/benefit analysis comparing the possible complications of the procedure versus the severity of the reason for needing TIPS. Child's class A and early Child's class B with a score 5–7 with moderately preserved hepatic function are considered low risk for TIPS. The MELD score was initially developed to predict short term mortality in patient undergoing TIPS, but is also a reliable to estimate one year survival. A MELD <14 has the best outcomes, while MELD >18 predicts poor outcome. In a patient with MELD >24 TIPS should be avoided unless it is used as a last resort to control active variceal bleeding. In a high risk patient a transplant center should be consulted prior to proceeding as decompensation may occur. The workup ideally uncovers any absolute contraindications and promotes discussion around relative contraindications, which are listed in Table 19.2.

**Table 19.2** Contraindications to TIPS

Absolute	Relative
Severe and progressive liver failure	Portal and hepatic vein thrombosis
Severe encephalopathy	Moderate pulmonary hypertension
Polycystic liver disease	Hepatopulmonary syndrome
Severe right-heart failure	Active infection
Severe pulmonary hypertension	Tumor in the shunt path

**Table 19.3** TTE findings in pathophysiology relevant to pre-TIPS evaluation

Pathophysiology	TTE Findings
RV Systolic Dysfunction	Tricuspid annular plane systolic excursion (TAPSE) < 2 Tricuspid annular systolic velocity (TASV) < 15 cm/s
RV Diastolic Dysfunction	Tricuspid E/A ratio < 0.8—impaired relaxation 0.8–2.1—pseudonormal filling >2.1—restrictive filling
Cirrhotic Cardiomyopathy	Blunted response to pharmacologic or exercise stress test Resting ejection fraction <55% Diastolic dysfunction: E/A <1.0, prolonged deceleration >200 ms, or prolonged isovolumetric relaxation time >80 ms
Pulmonary Hypertension	Mean pulmonary artery pressure >25 mmHg
Hepatopulmonary Syndrome	Positive “late” (after 5–6 beats) bubble study

## 19.5 Preprocedure Evaluation

Grading the degree of hepatic encephalopathy (HE), assessment of the heart with transthoracic echocardiography (TTE) plus bubble study with an emphasis on right heart function and right ventricular systolic pressure, and studies of coagulation are all needed prior to deciding on TIPS candidacy. (Table 19.3).

### 19.5.1 Cardiac Considerations

The high cardiac output state is worsened by TIPS secondary to a drop in systemic vascular resistance (SVR) and pulmonary hypertension is worsened as pulmonary vascular resistance (PVR) increases from both mechanical and neurohumoral reasons [33]. Even after shunt occlusion from thrombosis or planned reversal PVR remains high though all other hemodynamic parameters return to normal. Anticipation of this significant change in pulmonary artery pressure and increased right end diastolic volume is why TTE is so important. The assessment of the right ventricle is difficult since the morphology is not cylindrical and the systolic motion is both a spiral “towel wringing” motion along with a vertical compression. Therefore right ventricle function is assessed qualitatively. Diastolic function of both the right and left heart is required as the hemodynamic changes that occur with TIPS can exacerbate the consequences of baseline diastolic dysfunction or underlying cirrhotic cardiomyopathy. The ability of the chambers to fill during diastole is impaired when the heart rate increases and the extra volume adds to the pressure transmitted to the pulmonary veins, worsening both pulmonary hypertension and, initially, hepatopulmonary syndrome. Cirrhotic cardiomyopathy is usually silent in stable conditions as the reduction in afterload suppresses manifestations of heart failure, but publications showing post-TIPS complications of overt heart failure and pulmonary edema suggest its presence as a risk factor [79, 80].

### 19.5.2 Hemostasis Considerations

The coagulation studies and their clinical importance prior to TIPS is somewhat controversial. As stated elsewhere in this chapter traditional markers of surgical bleeding are not as predictive in patients with end-stage liver disease. Thromboelastography (TEG) has been shown to be more accurate in guiding transfusion in cirrhotic patients as it provides a more global picture and can even uncover those patients who are hypercoagulable in the presence of a prolonged prothrombin time. A dedicated liver transplant anesthesiology team also lowers the transfusion rates second to an increased fund of knowledge of end-stage liver disease physiology and an increased comfort in management of intraoperative hemostasis [81]. Interventional radiologists who will be assuming the procedural risk are often loathe to performing TIPS without a corrected INR and platelets higher than severe cirrhotic patients usually have. Their hesitation is understandable since the bleeding is hidden within the black box of the abdomen. However fresh frozen plasma and platelet transfusion is not a panacea and could cause unintended harm. Drs. Wu and Nguyen showed in 2010 that hospitalized patients, age 45 or younger, with liver disease had an increased prevalence of venous thromboembolism compared with controls [82]. This translated into an increase in-hospital mortality from 9.8% in patients with no liver disease and VTE to 18.6% in patients with liver disease and VTE. In patients less than 45 years old going for TIPS a lower extremity duplex scan for DVTs should be considered prior to correction of INR and platelets. Especially given that even in end-stage liver disease patients with significant coagulopathy, post invasive procedure bleeding is rare [83].

## 19.6 Perioperative Management

### 19.6.1 Intravascular Volume Management

There have been several studies in cirrhotic patients undergoing TIPS looking at the effect of both volume expansion

and volume restriction on postprocedure hemodynamics and complications. Given that TIPS acutely increases the circulating volume it has been proposed that fluid restriction might reduce the degree of sudden hemodynamic shifts. On balance the literature shows no difference in immediate episodes of heart failure, even with acute volume expansion before TIPS in patients with diastolic dysfunction [84].

### 19.6.2 Postoperative Care

TIPS patients are routinely cared for in the intensive care unit or a step-down unit overnight to monitor for signs of heart failure or, more commonly, worsening HE. Typically patients will respond to increased therapies for HE, but refractory HE or a decline to Grade 4 HE may necessitate a reversal of the TIPS.

## 19.7 Cholecystectomy

Gallstone disease is the most common extrahepatic surgery performed in patients with cirrhotic liver disease, accounting for approximately 60% of non-transplant operations in this population [6]. Up to 29% of patients with a long history of cirrhosis have gallstone disease, which is twice that of the general population [85, 86]. Child's class B and C is associated with a greater risk of developing cholelithiasis secondary to a host of factors – increased change in bile composition, worsening gallbladder hypomotility, and increased plasma concentrations of intestinal relaxing peptides [87]. Fortunately, the majority of gallstones are “silent” or asymptomatic and are discovered during ultrasonography (US) for other abdominal indications. Historically there has been a higher incidence of cholecystectomies performed in cirrhotic patients [88, 89]. Whether it is secondary to an increased detection from frequent surveillance, cholecystectomy recommended at a higher rate in altered liver function tests, or a new finding of latent cirrhosis during surgery, cholecystectomy in a cirrhotic patient carries an odds ratio for perioperative mortality of 8.47 [90]. Open cholecystectomy (OC) is rarely performed as the complication rate, even in the general population, is higher and carries a longer length of stay and recovery than laparoscopic cholecystectomy (LC).

### 19.7.1 Preoperative Assessment

Whether CTP class or MELD score is used to predict perioperative risk, an assessment must be done to decide whether definitive treatment or temporization is appropriate. Child class A and B patients have no increase in mortality over the general population (0–1%) but a sharp increase in morbidity

(5–10% versus 1.9%) [29, 91]. Patients with a MELD score <8 have the same mortality risk as the general population, but that increases to 6% at a MELD of  $\geq 8$ . As seen in the earlier part of this chapter any one point increase in MELD correlates with a 1% increase in mortality up to a MELD of 20. Therefore a risk-benefit analysis should be done with ever increasing MELD scores. The mortality for laparoscopic cholecystectomy in Child's class C is anywhere from 23–50%, which is typically seen as too high a risk and medical treatment and/or percutaneous cholecystostomy is advised. Lastly, the presence of common bile duct (CBD) stones alters the morbidity and mortality to 29% and 9.6% respectively for laparoscopic cholecystectomy in Child's A/B patients. Endoscopic sphincterotomy (ES) is recommended to decrease the morbidity and mortality prior to surgery, but even then the mortality risk remains elevated at 7% [1]. In Child's class C the risk of bleeding with ES is still unacceptably high and therefore balloon endoscopic sphincteroplasty should be considered.

### 19.7.2 Perioperative Management

The effect of liver disease on anesthetic agents and vice versa has been discussed elsewhere in this chapter. The choice of whether to use anxiolysis, type of induction agents, amount of narcotics, etc. should be placed in the context of severity of each patient's liver disease. However, even with the best management 15% of patients will have a deterioration of their liver disease after LC, which has been shown to return to baseline by one month [92]. In the immediate postoperative period possible increased ascites, bleeding at the umbilical port site, and port site infection should be assessed daily. Due to the increased risk of bleeding in patients with portal hypertension a subhepatic drain should be placed to facilitate recognition of intraabdominal bleeding in the immediate postoperative period.

## 19.8 Endoscopic Procedures

Upper and lower endoscopy is performed repeatedly in end-stage liver disease to monitor for and treat sequelae of portal hypertension. To reduce discomfort these procedures are often done under sedation. In the general population either propofol or midazolam, with or without narcotics, is routinely used. Midazolam's rapid onset and anterograde amnesic effects make it superior to older benzodiazepines. However, the decreased hepatic blood flow and altered hepatic function and the presence of hepatic encephalopathy alter its utility in the ESLD population. Patients with subclinical HE diagnosed by neurocognitive testing (NCT) did not have worse NCT scores after having propofol for their



endoscopy procedure as compared to worsening NCT scores and increased length of recovery in ESLD patients given midazolam. Midazolam has been shown to increase time to discharge by 80 min on average and by as much as 120 min in comparison to propofol [93]. During esophagogastroduodenoscopy (EGD) and endoscopic retrograde cholangiopancreatography (ERCP) the endoscopist is able to suction any residual gastric fluid and help prevent aspiration. However, each patient's aspiration risk and the positioning of the patient for the procedure should be taken into consideration when deciding on intubation for airway protection. ERCP is often performed with the patient in the prone position which makes airway management difficult and puts any ESLD patient at risk if they have ascites. Patients with ascites have delayed gastric emptying even after paracentesis [94]. This is regardless of Child's class and may be 1½ times longer than control groups.

### 19.8.1 Perioperative Management

The preoperative assessment for endoscopic procedures in ESLD patients differs from non-ESLD patients in regards to preprocedure fasting, planning for increased airway protection during ERCP, and consideration of increased bleeding risk in procedures where incisions and mucosal invasion may occur. In decompensated cirrhotic patients avoidance of benzodiazepines is recommended and propofol with or without low doses of fentanyl is considered preferable. There is no difference in fluid management from controls.

## 19.9 Summary and Recommendations

- In patients with acute liver disease, elective surgery should be postponed until the cause of the disease is identified.
- In patients with chronic liver disease, the perioperative risk is related to the severity of the liver disease and the site of the surgical procedure.
- Elective high-risk procedures in patients with Child's C cirrhosis or MELD scores of 20 or higher should be deferred until after liver transplantation.
- When patients with severe disease require emergency surgery they should be evaluated for minimally invasive and less extensive surgical alternatives.
- Transfer to a liver transplant center should be considered for patients with moderate or severe liver disease in order to facilitate transplant listing in the event of decompensation.
- Preoperative medical management should focus on treating infection, optimizing blood volume and renal status, and minimizing ascites and encephalopathy.

- Routine administration of prophylactic plasma in an attempt to correct INR abnormalities should be avoided, as volume loading is associated with increases in portal pressure that may worsen bleeding.
- While no anesthetic technique is universally preferred, the presence of coagulopathy may contraindicate neuraxial regional techniques. The chosen technique should be designed to maintain splanchnic, hepatic, and renal perfusion.
- Patients undergoing TIPS should have a pre-procedure TTE specifically looking at right heart function.
- Avoid unnecessary platelet and plasma transfusion prior to percutaneous interventions.
- In patients with ascites delayed gastric emptying should be presumed and airway protection maximized.
- Estimation of MELD or Child's Class prior to surgery should occur and be used in deciding on definitive versus temporizing procedures.

## 19.10 Questions and Answers

A 62 year old man with alcoholic hepatitis presents for cholecystectomy. He undergoes paracentesis once a month and has grade 1 hepatic encephalopathy at baseline. His other sequelae of ESLD include hepatorenal syndrome, esophageal varices, and GERD. TTE with bubble study reveals moderate diastolic dysfunction, a TAPSE of 2.0, and hepatopulmonary syndrome. Preoperative labs are as follows: sodium 132, potassium 2.8, bicarb 20, creatinine 2.3, bilirubin 3.5, hemoglobin 9.8, platelets 46, INR 2.2.

1. What is this patient's 30-day mortality risk after surgery?  
Risk for this patient must take into account both the ASA status and the MELD-Na. The ASA status for this patient is IV as he has severe systemic disease which is a constant threat to life. An ASA of IV has a MELD equivalent of 5 points, which is then added to the MELD-Na. The MELD-Na = MELD - Na -  $[0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$ . For this patient MELD-Na is 30, so total MELD is 35. This imparts a 50% mortality risk to this patient.
2. What is the risk of performing this surgery at an institution without a liver transplant program?  
Patients with a high MELD have an increased risk of acute hepatic failure after surgery. This may necessitate an expedited evaluation for transplant. Acute on chronic liver failure has an increased risk for multiple complications including infection, respiratory failure, bleeding, and death. Surgery in patients with high MELD should

be performed at a transplant center to have access to specialized postoperative care and possible transplantation.

3. The general surgeon would like to transfuse platelets and fresh frozen plasma to increase platelets >50 and normalize the INR prior to surgery. They ask for your opinion on managing the patient's presumed coagulopathy. What would you advise?

The balance of coagulation and thrombolysis in ESLD patients is skewed and standard tests are not as reflective of surgical hemostasis. Since INR does not measure Protein C and S, which is also decreased in ESLD, it is less useful in decisions to transfuse. Viscoelastic testing would help see the balance of clotting versus thrombolysis. If transfusion was needed the overall volume status of the patient should be evaluated and prothrombin complex concentrate considered to prevent overload. In addition a fibrinogen level should be checked and either cryoprecipitate or fibrinogen concentrate should be given to maintain levels greater than 1.5 g/L.

## References

1. Bhangui P, Laurent A, Amathieu R, et al. Assessment of risk for non-hepatic surgery in cirrhotic patients. *J Hepatol*. 2012;57(4):874–84.
2. Franco D, Charra M, Jeambrun P, et al. Nutrition and immunity after peritoneovenous drainage of intractable ascites in cirrhotic patients. *Am J Surg*. 1983;146(5):652–7.
3. Rabinovitz M, Schade RR, Dindzans V, et al. Prevalence of duodenal ulcer in cirrhotic males referred for liver transplantation. Does the etiology of cirrhosis make a difference? *Dig Dis Sci*. 1990;35(3):321–6.
4. Castaing D, Houssin D, Lemoine J, et al. Surgical management of gallstones in cirrhotic patients. *Am J Surg*. 1983;146(3):310–3.
5. Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology*. 2007;132(4):1261–9.
6. Csikesz NG, Nguyen LJ, Tseng JF, et al. Nationwide volume and mortality after elective surgery in cirrhotic patients. *J Am Coll Surg*. 2009;208(1):96–103.
7. Aranha GV, Sontag SJ, Greenlee HB. Cholecystectomy in cirrhotic patients: a formidable operation. *Am J Surg*. 1982;143(1):55–60.
8. Garrison RN, Cryer HM, Howard DA, et al. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. *Ann Surg*. 1984;199(6):648.
9. Mansour A, Watson W, Shayani V, et al. Abdominal operations in patients with cirrhosis: still a major surgical challenge. *Surgery*. 1997;122(4):730–5. discussion 735–736.
10. Neeff H, Mariaskin D, Spangenberg H-C, et al. Perioperative mortality after non-hepatic general surgery in patients with liver cirrhosis: an analysis of 138 operations in the 2000s using child and MELD scores. *J Gastrointest Surg*. 2011;15(1):1–11.
11. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864–71.
12. Freeman RB, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl*. 2002;8(9):851–8.
13. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359:1018–26.
14. Biggins SW. Use of serum sodium for liver transplant graft allocation: a decade in the making, now is it ready for primetime? *Liver Transpl*. 2015;21:279–81.
15. Northup PG, McMahon MM, Ruhl AP. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. *Am J Gastroenterol*. 2006;101:1524–8.
16. Ziser A, Plevak DJ, Wiesner RH, et al. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. *Anesthesiology*. 1999;90(1):42–53.
17. Powell-Jackson P, Greenway B, Williams R. Adverse effects of exploratory laparotomy in patients with unsuspected liver disease. *Br J Surg*. 1982;69(8):449–51.
18. Rizvon MK, Chou CL. Surgery in the patient with liver disease. *Med Clin North Am*. 2003;87(1):211–27.
19. Friedman LS. Surgery in the patient with liver disease. *Trans Am Clin Climatol Assoc*. 2010;121:192–205.
20. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (NY)*. 2012;8(8):513–20.
21. Schemel WH. The unexpected hepatic dysfunction found by multiple laboratory screening. *Anesth Analg*. 1976;55(6):810–2.
22. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med*. 2000;342(17):1266–71.
23. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepatol*. 2016;64(3):717–35.
24. Tripodi A, Massimo P, Veena C, et al. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology*. 2006;44(2):440–5.
25. Lisman T, Bakhtiari K, Pereboom IT, et al. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation test. *J Hepatol*. 2010;53(3):355–61.
26. Viegas O, Stoelting RK. LDH5 changes after cholecystectomy or hysterectomy in patients receiving halothane, enflurane, or fentanyl. *Anesthesiology*. 1979;51(6):556–8.
27. Shaikh AR, Muneer A. Laparoscopic cholecystectomy in cirrhotic patients. *JSLs*. 2009;13(4):592–6.
28. Currò G, Iapichino G, Melita G, et al. Laparoscopic cholecystectomy in child-pugh class C cirrhotic patients. *JSLs*. 2005;9(3):311–5.
29. Yeh CN, Chen MF, Y.Y. Laparoscopic cholecystectomy in 226 cirrhotic patients. *Surg Endosc*. 2002;16(11):1583–7.
30. Laurence JM, Tran PD, Richardson AJ, et al. Laparoscopic or open cholecystectomy in cirrhosis: a systematic review of outcomes and meta-analysis of randomized trials. *HPB*. 2012;14(3):153–61.
31. Cheng Y, Xiong X-Z, Wu S-J, et al. Laparoscopic vs. open cholecystectomy for cirrhotic patients: a systematic review and meta-analysis. *Hepatogastroenterology*. 2011;59(118):1727–34.
32. Azoulay D, Buabse F, Damiano I, et al. Neoadjuvant transjugular intrahepatic portosystemic shunt: a solution for extrahepatic abdominal operation in cirrhotic patients with severe portal hypertension. *J Am Coll Surg*. 2001;193(1):46–51.
33. Van der Linden P. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. *Hepatology*. 1996;23(5):982–7.
34. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems: transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology*. 1998;28(2):416–22.
35. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness?: A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134(1):172–8.

36. Niemann CU, Feiner J, Behrends M, et al. Central venous pressure monitoring during living right donor hepatectomy. *Liver Transpl*. 2007;13(2):266–71.
37. Spier BJ, Larue SJ, Teelin TC, et al. Review of complications in a series of patients with known gastro-esophageal varices undergoing transesophageal echocardiography. *J Am Soc Echocardiogr*. 2009;22(4):396–400.
38. Myo Bui CC, Worapot A, Xia W, et al. Gastroesophageal and hemorrhagic complications associated with intraoperative transesophageal echocardiography in patients with model for end-stage liver disease score 25 or higher. *J Cardiothorac Vasc Anesth*. 2015;29(3):594–7.
39. Markin NW, Sharma A, Grant W, et al. The safety of transesophageal echocardiography in patients undergoing orthotopic liver transplantation. *J Cardiothorac Vasc Anesth*. 2015;29(3):588–93.
40. Samama CM, Djoudi R, Lecompte T, French Health Products Safety Agency (AFSSAPS) Expert Group, et al. Perioperative platelet transfusion. Recommendations of the french health products safety agency (AFSSAPS) 2003. *Minerva Anesthesiol*. 2006;72(6):447–52.
41. Rahe-Meyer N, Solomon C, Winterhalter M, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *J Thorac Cardiovasc Surg*. 2009;138(3):694–702.
42. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):1.
43. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the european society of anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270–382.
44. Youssef W. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. *Am J Gastroenterol*. 2003;98(6):1391–4.
45. Amarapurkar PD, Amarapurkar DN. Management of coagulopathy in patients with decompensated liver cirrhosis. *Int J Hepatol*. 2011;2011:1–5.
46. Raschke RA, Curry SC, Rempe S, et al. Results of a protocol for the management of patients with fulminant liver failure. *Crit Care Med*. 2008;36(8):2244–8.
47. Sorensen B, Spahn DR, Innerhofer P, et al. Clinical review: prothrombin complex concentrates – evaluation of safety and thrombogenicity. *Crit Care*. 2011;15(1):201.
48. Theodoulou A, Berryman J, Nathwani A, et al. Comparison of cryoprecipitate with fibrinogen concentrate for acquired hypofibrinogenemia. *Transfus Apher Sci*. 2012;46(2):159–62.
49. Ahmed S, Harrity C, Johnson S, et al. The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage—an observational study: fibrinogen concentrate in major obstetric haemorrhage. *Transfus Med*. 2012;22(5):344–9.
50. Servin F, Desmonts JM, Haberer JP, et al. Pharmacokinetics and protein-binding of propofol in patients with cirrhosis. *Anesthesiology*. 1988;69(6):887–91.
51. Trouvin JH, Farinotti R, Haberer J, et al. Pharmacokinetics of midazolam in anesthetized cirrhotic patients. *BJA*. 1988;60(7):762–7.
52. MacGilchrist AJ, Birnie GG, Cook A, et al. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. *Gut*. 1986;27(2):190–5.
53. Tegeder I, Lötsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. *Clin Pharmacokinet*. 1999;37(1):17–40.
54. Hunter JM, Parker CJ, Bell CF, et al. The use of different doses of vecuronium in patients with liver dysfunction. *Br J Anaesth*. 1985;57(8):758–64.
55. Magorian T, Wood P, Caldwell J, et al. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesth Analg*. 1995;80(4):754–9.
56. Cahill PA. Vasoconstrictor responsiveness of portal hypertensive vessels. *Clin Sci*. 1999;96(1):3–4.
57. Cahill PA, Redmond EM, Sitzmann JV. Endothelial dysfunction in cirrhosis and portal hypertension. *Pharmacol Ther*. 2001;89:273–93.
58. Wagener G, Galina K, Moury M, Landry DW, et al. Vasopressin deficiency and vasodilatory state in end-stage liver disease. *J Cardiothorac Vasc Anesth*. 2011;25(4):665–70.
59. de Mattos A, Angelo. Current indications for the use of albumin in the treatment of cirrhosis. *Ann Hepatol*. 2011;10(Suppl 1 (May)):S15–20.
60. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. *J Clin Exp Hepatol*. 2014;4(4):302–11.
61. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49(6):2087–107.
62. Terg R, Adrian G, Mariano C, et al. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. *Liver Int*. 2009;29(3):415–9.
63. Schindler E, Müller M, Zickmann B, et al. Blood supply to the liver in the human after 1 MAC desflurane in comparison with isoflurane and halothane. *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie: AINS*. 1996;31(6):344–8.
64. Frink EJ. The hepatic effects of sevoflurane. *Anesth Analg*. 1995;81(6 Suppl):S46–50.
65. Njoku D, Laster MJ, Gong DH, et al. Biotransformation of halothane, enflurane, isoflurane, and desflurane to trifluoroacetylated liver proteins: association between protein acylation and hepatic injury. *Anesth Analg*. 1997;84(1):173–8.
66. Obata R, Bito H, Ohmura M, et al. The effects of prolonged low-flow sevoflurane anesthesia on renal and hepatic function. *Anesth Analg*. 2000;91(5):1262–8.
67. Watkins PB, Seeff LB. Drug-induced liver injury: summary of a single topic clinical research conference. *Hepatology*. 2006;43(3):618–31.
68. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. *Br J Anaesth*. 1987;59(1):3–13.
69. Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ*. 1992;305(6854):613–6.
70. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. *Curr Opin Anaesthesiol*. 2008;21(5):544–51.
71. Kennedy WF, Everett GB, Cobb LA, et al. Simultaneous systemic and hepatic hemodynamic measurements during high peridural anesthesia in normal man. *Anesth Analg*. 1971;50(6):1069–78.
72. Meierhenrich R, Wagner F, Schutz W, et al. The effects of thoracic epidural anesthesia on hepatic blood flow in patients under general anesthesia. *Anesth Analg*. 2009;108(4):1331–7.
73. Tanaka N, Nagata N, Hamakawa T, et al. The effects of dopamine on hepatic blood flow in patients undergoing epidural anesthesia. *Anesth Analg*. 1997;85(2):286–90.
74. Hildebrand LB, Krejci V, Sigurdsson GH. Effects of dopamine, dobutamine, and dopexamine on microcirculatory blood flow in the gastrointestinal tract during sepsis and anesthesia. *Anesthesiology*. 2004;100(5):1188–97.
75. Dumitrescu G, Januszkiewicz A, Ågren A, et al. The temporal pattern of postoperative coagulation status in patients undergoing major liver surgery. *Thromb Res*. 2015;136(2):402–7.
76. McDonnell JG, O'Donnell B, Curley G, et al. The analgesic efficacy of transversus abdominis plane block after abdominal sur-

- gery: a prospective randomized controlled trial. *Anesth Analg*. 2007;104(1):193–7.
77. Boyer T, Haskal Z. AASLD practice guidelines: the role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. *Hepatology*. 2010;51(1):1–16.
78. Ripamonti R, Ferri H, Alonzo M, et al. Transjugular intrahepatic portosystemic shunt-related complications and practical solutions. *Semin Intervent Radiol*. 2006;23(2):165–76.
79. Braverman AC, Steiner MA, Picus D, et al. High output congestive heart failure after transjugular intrahepatic portal-systemic shunting. *Chest*. 1995;107(5):1467–9.
80. Salerno F. Humoral and cardiac effects of TIPS in cirrhotic patients with different “effective” blood volume. *Hepatology*. 2003;19:129–32.
81. Hevesi ZG, Lopukhin SY, Mezrich JD, et al. Designated liver transplant anesthesia team reduces blood transfusion, need for mechanical ventilation, and duration of intensive care. *Liver Transplant*. 2009;15(5):460–5.
82. Wu H, Nguyen G. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol*. 2010;8:800–5.
83. DePietri L, Bianchini M, Montalti R, et al. Thromboelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. *Hepatology*. 2016;63:566–73.
84. Fili D, Falletta C, Luca A, et al. Circulatory response to volume expansion and TIPS: relationship with diastolic dysfunction. *Dig Liver Dis*. 2015;47:1052–8.
85. Acalovschi M. Gallstones in patients with liver cirrhosis: Incidence, etiology, clinical and therapeutical aspects. *World J Gastroenterol*. 2014;20(23):7277–85.
86. Conte D, Fraquelli M, Lodi L, et al. Close Relation between cirrhosis and gallstones: cross-sectional and longitudinal survey. *Arch Intern Med*. 1999;159:49–52.
87. Barreca T, Franceschini R, Cataldi A, et al. Plasma somatostatin response to an oral mixed test meal in cirrhotic patients. *J Hepatol*. 1991;12:40–4.
88. Barbara L, Sama C, Morselli AM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology*. 1987;7:913–7.
89. Maggi A, Solenghi D, De Fazio C, et al. Prevalence and incidence of cholelithiasis in patients with liver cirrhosis. *Ital J Gastroenterol Hepatol*. 1997;29:330–5.
90. Rai R, Nagral S, Nagral A. Surgery in a patient with liver disease. *J Clin Exp Hepatol*. 2012;2:238–46.
91. Duca S, Bala O, Al-Hajjar N, et al. Laparoscopic cholecystectomy: incidents and complications. A retrospective analysis of 9542 consecutive laparoscopic operations. *Hepatobiliary*. 2003;5(3):152–8.
92. Palanivelu C, Rajan PS, Jani K, et al. Laparoscopic cholecystectomy in cirrhotic patients; the role of subtotal cholecystectomy and its variants. *J Am Coll Surg*. 2006;203:145–51.
93. Iyad K, Nseir W, Alexandrov O, Mysh V, et al. Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: a randomized controlled study. *J Hepatol*. 2011;54(1):72–7.
94. Schoonjans R, Van Vlem B, Vandamme W, et al. Gastric emptying of solids in cirrhotic and peritoneal dialysis patients: influence of peritoneal volume load. *Eur J Gastroenterol Hepatol*. 2002;14:395–8.



Mark T. Keegan

## Abstract

For a liver transplant (LT) program to be successful, the support of a high-quality critical care service is essential. LT recipients, candidates, and potential candidates, are frequent consumers of intensive care unit (ICU) resources. Among multiple specialists caring for patients who require LT, intensivists play a unique role by providing continuous bedside presence to deliver evidence—based therapeutic interventions that provide support for multiple organs, while taking an holistic view of the patient [1–3]. Many factors will determine a patient’s ultimate outcome after LT. Whether an ICU stay is brief (after a “routine” LT, for example) or prolonged (because of the need for critical care support pre-operatively in addition to postoperatively, for example), delivery of high-quality ICU care is a key element of the hospital infrastructure required to deliver excellent outcomes.

## Keywords

Liver transplantation • Perioperative management • Intensive care

## 20.1 Introduction

For a liver transplant (LT) program to be successful, the support of a high-quality critical care service is essential. LT recipients, candidates, and potential candidates, are frequent consumers of intensive care unit (ICU) resources. Among multiple specialists caring for patients who require LT, intensivists play a unique role by providing continuous bedside presence to deliver evidence—based therapeutic interventions that provide support for multiple organs, while taking an holistic view of the patient [1–3]. Many factors will determine a patient’s ultimate outcome after LT. Whether an ICU stay is brief (after a “routine” LT, for example) or prolonged (because of the need for critical care support pre-operatively in addition to postoperatively, for example), delivery of high-quality ICU care is a key element of the hospital infrastructure required to deliver excellent outcomes.

The intensity and duration of ICU-level support varies according to the severity of pre-transplant illness and the nature of the intraoperative course. The character of the ICU stay for LT candidates and recipients has evolved over the past three decades. At the dawn of the LT era the operative procedure lasted many, many hours and was associated with requirements for huge volumes of blood and blood products. This translated into a prolonged and difficult post-transplant ICU course. Advances in surgical and anesthetic techniques, however, have streamlined the intraoperative course, to the point that—although it is still a major undertaking that challenges the surgical and anesthetic teams—the intraoperative portion of the LT experience is now “routine”, allowing modifications of practice to decrease perioperative complications and costs. Living donor liver transplantation (LDLT) has allowed more time for optimization of recipients prior to transplantation and the “fast tracking” movement has shortened the duration of postoperative ICU care. These factors have led to a decrease in the duration of postoperative mechanical ventilation and a limitation of the number and intensity of postoperative ICU interventions required in LT recipients. At some LT centers, selected recipients who have had an unremarkable intraoperative course are

M.T. Keegan, MB, MRCPI, MSc, DABA  
Division of Critical Care, Department of Anesthesiology,  
Mayo Clinic, Charlton 1145, 200 1st Street SW, Rochester,  
MN 55905, USA  
e-mail: [keegan.mark@mayo.edu](mailto:keegan.mark@mayo.edu)

extubated at the end of the procedure and are managed in an intermediate care area rather than the ICU. Of course, some patients still provide very difficult intellectual and physical challenges for the operating room (OR) team and these challenges continue into the ICU, but, in general, the immediate postoperative care has become easier over time.

This may be changing again. In the era of the use of the Model for End-Stage Liver Disease (MELD) for donor organ allocation and an increased acceptance of expanded criteria donors, the acuity of transplant candidates and recipients have increased [4, 5]. Fewer outpatients come to the hospital on the day of their transplant, but rather are taken to the OR from the general ward or the ICU [5–7]. LT recipients in the MELD era have a higher severity of illness, are more acutely ill, have a greater number of pre-transplant comorbidities, more deranged baseline laboratory test values, and a tendency for greater requirements for intraoperative vasoactive and transfusion support. Such patients are also more likely to have required the services of the ICU preoperatively because of respiratory failure, hemodynamic instability, or higher degrees of porto-systemic encephalopathy. These factors may result in a prolongation of ICU stay. Thus “the OR experience of future LT recipients may simply be a brief period between two prolonged ICU stays” [8]. The role of postoperative ICU care in some cases may be one of rehabilitation and chronic ventilation in patients who are extremely debilitated prior to transplantation.

LT recipients are usually cared for in general ICUs, although in larger institutions transplant-specific (not necessarily *liver* transplant specific) ICUs are common [9]. The level of intensivist engagement in the care of ICU patients is country-, institution- and unit-specific. Critical care is very expensive, resources are under strain and concern has been expressed regarding long-term ICU workforce issues [10]. Transplant programs may seek to decrease the time their patients spend in the ICU to decrease costs while at the same time transplanting sicker patients. Collaboration between the transplant and critical care communities is essential.

This chapter will focus on the intraoperative management and early postoperative ICU care of adult patients undergoing LT, to include both those undergoing a “straightforward” LT and those for whom a preoperative requirement for ICU support complicates perioperative management.

Although this chapter will take, in part, an organ-based approach to the management of a patient, one must not forget that a recipient of a LT is more than simply the sum of individual organ systems and that patient and family psychological and social aspects need to be considered in patient management.

## 20.2 Intraoperative Management

Although the specifics vary by institution the key LT intraoperative personnel include the surgical team, the anesthesia team, and the “support” team. A principal surgeon, at least one

assistant surgeon, a scrub nurse, and a circulating nurse make up the surgical team. The anesthesia team is comprised of an anesthesiologist, typically aided by a nurse anesthetist and/or anesthesia fellow and/or resident. It is common for institutions with large LT programs to have a dedicated LT call team or to be part of a larger “transplant” team. The “support” team includes essential personnel such as those who staff the transfusion medicine service (including the “blood bank” and intraoperative autotransfusion), clinical laboratory staff, and OR pharmacy personnel. Other perioperative staff may include personnel with responsibilities for radiology, respiratory therapy, clinical monitoring and dialysis [11]. While providing perioperative critical care, intensivists work in collaboration with the anesthesia and surgical teams. In addition, they often participate in candidate evaluation, especially for those who are critically ill at the time of the proposed transplant.

### 20.2.1 Phases of the LT Procedure

Intraoperatively, LT is divided into three phases, as described in Table 20.1 [12–14]. Reperfusion of the allograft liver is a relatively brief period that distinguishes the anhepatic phase from the neohepatic phase (aka post-anhepatic phase) and tends to be the time during which most instability occurs.

### 20.2.2 Anesthesia Technique

The LT procedure is performed under general anesthesia. Induction and maintenance are achieved using agents that provide anesthesia, amnesia, analgesia and optimal surgical operating conditions, being cognizant of the metabolic derangements that occur in patients with liver disease, and while attempting to minimize end-organ compromise [12–14]. Although patients are usually not extubated at the end of the procedure (see below), anesthetic drugs and doses are chosen to allow relatively rapid emergence at the completion of surgery, either in the OR or, more commonly, in the ICU [15]. Midazolam and fentanyl are typically administered intravenously followed by induction with propofol or etomidate or ketamine. In patients who come to the OR from the ICU already intubated inhalation induction using a volatile agent through the endotracheal tube (ETT) is the preferred method. The desire to maintain hemodynamic stability must be balanced against the risk of aspiration when considering whether or not a rapid sequence induction and intubation should be employed. For maintenance during the procedure, a “balanced” anesthesia technique is typically used, employing a combination of intravenous opiates (usually fentanyl at a dose of up to 20 mcg/kg for the case), volatile agent (typically isoflurane or sevoflurane) and non-depolarizing muscle relaxants. Cisatracurium or atracurium are the neuromuscular blocking agents of choice because they are metabolized independently of the liver and kidneys.

**Table 20.1** Phases of the liver transplant procedure with associated features. From Keegan MT, Kramer DJ. Perioperative care of the liver transplant patient. *Crit Care Clin* 32 (2016) 453–473

Phase	Pre-anhepatic	Anhepatic	Reperfusion	Neohepatic
Timing	From incision to isolation of native liver from circulation	From isolation of native liver from circulation to reperfusion	A brief event at which the new liver is introduced into the patient's circulation	From reperfusion to the end of the procedure
Features	<ul style="list-style-type: none"> <li>• Anesthesia induction</li> <li>• Line placement Skin incision</li> <li>• Dissection to allow removal of diseased liver</li> <li>• Obvious and insidious blood losses</li> <li>• Fluid shifts</li> <li>• Potential compression of native vessels during dissection</li> <li>• Worsening of pre-existing coagulopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Isolation of native liver from circulation</li> <li>• Removal of diseased liver</li> <li>• Implantation of new liver</li> <li>• Decrease in venous return (degree dependent on technique. Modern “piggyback technique” affects venous return less than complete IVC occlusion technique)</li> <li>• Progressive coagulopathy</li> <li>• Progressive metabolic acidosis</li> <li>• Hypocalcemia</li> </ul>	<ul style="list-style-type: none"> <li>• Introduction of new liver into the circulation</li> <li>• Time of most instability</li> <li>• Potassium load, cytokine load, emboli, cold fluid</li> <li>• Hypotension common</li> <li>• Intracranial pressure may rise</li> <li>• Pulmonary hypertension may worsen</li> <li>• Arrhythmias</li> <li>• Coagulopathy may worsen</li> </ul>	<ul style="list-style-type: none"> <li>• From reperfusion to end of procedure</li> <li>• Reconstruction of hepatic artery</li> <li>• Construction of biliary anastomoses</li> <li>• New liver begins to function</li> <li>• Hemostasis</li> <li>• Continuing correction of coagulopathy, metabolic and acid base disorders</li> <li>• Optimization of cardiovascular parameters</li> <li>• Preparation for emergence</li> </ul>

In patients with acute liver failure (ALF) in whom intracranial hypertension is a concern (and in the rare circumstances of a patient with a predisposition to malignant hyperthermia) a total intravenous anesthetic (TIVA) technique is used [16–19]. For TIVA, typically a propofol infusion is used in place of the volatile anesthetic. Many anesthesiologists use a measure of cerebral function such as processed electroencephalogram when TIVA is being employed.

### 20.2.3 Vascular Access, Monitors, and Other Considerations

Adequate vascular access is essential for the LT procedure, which may be associated with major blood loss and hemodynamic derangements. For similar reasons, monitoring in excess of standard American Society of Anesthesiologists (ASA) monitors is placed. Depending on the condition of the patient and institutional practice, vascular access may be placed before or after induction of anesthesia. One or more large bore peripheral venous catheters (e.g. “trauma catheter”) should be placed and connected to a rapid infusion device. Multiple units of packed red blood cells and blood products may be placed into the reservoir of a typical rapid infusion device and administered simultaneously at high flow rates. Such devices usually allow high flow infusion of fluids and blood products with concomitant warming and debris/air filtering. The facility for fluid bolus administration is also available in such devices. Platelets and cryoprecipitate are usually administered by a different route as they can cause coagulation and malfunction of rapid infusion device systems.

Arterial catheters are usually placed at both radial and brachial (occasionally femoral) sites to allow for both continuous blood pressure monitoring and arterial blood sampling for laboratory analyses. Large bore central venous access is obtained, typically by cannulation of the internal jugular vein

and placement of an introducer and pulmonary artery catheter (PAC). Oximetric PACs are often used. A continuous cardiac output monitor may be used instead of, or in addition to a PAC. If peripheral access is suboptimal or if veno-veno bypass (less commonly used now) is planned, additional large bore central venous access is placed. Transesophageal echocardiography is used routinely in some centers and on occasions in others. Intraoperatively, maintenance of patient temperature is important for multiple reasons, so upper and lower warming blankets are usually placed.

To counteract volatile-anesthetic-induced vasodilation in patients who already have decreased systemic vascular resistance due to their liver disease, norepinephrine (NE) is commonly administered. (Dopamine was used for similar purposes in the past, but is less commonly administered now). Maintenance fluid is usually a non-lactate buffered balanced electrolyte crystalloid (e.g. Plasmalyte®) Crystalloids are supplemented with colloids, such as 5% or 25% albumin solutions which allows resuscitation with less total volume and replaces ascitic fluid lost during surgery, albeit at the expense of a relatively high sodium load.

Transfusion requirements during LT surgery have decreased over time so the standard surgical blood order (the number of units routinely prepared for a given surgery) has also decreased [20]. Nonetheless, the need for massive transfusion is still common and LT programs could not be successful without reliable and efficient transfusion medicine support. Except for cases in which malignancy or infection is present, autotransfusion is used. Also known as “cell saver” autotransfusion is a process whereby blood suctioned from the surgical field is removed of debris and non-erythrocyte matter in the OR and packaged similarly to banked red blood cell units ready to be infused back into the patient. Massive transfusion may be required. Consequences of such large volume transfusion include dilutional coagulopathy, citrate intoxication leading to hypocalcemia, hyperkalemia, and hypothermia.

Intraoperatively, multiple measurements of electrolytes (watching especially for hyperkalemia, hypocalcemia and the trend in serum sodium), glucose, complete blood count, coagulation parameters and arterial blood gases are performed. This requires the availability of a clinical chemistry laboratory, in proximity to the OR, with a short processing and reporting time.

### 20.3 Immediate Postoperative Care

At the completion of the LT procedure the patient usually remains intubated and ventilated and is sedated (typically with propofol) and transferred directly to the ICU [21]. As discussed below, however, this is not always the case, and in some centers, selected patients are managed immediately postoperatively in the post-anesthesia recovery unit (PACU) and subsequently a progressive care unit (PCU), thus bypassing the ICU. Unless specifically addressed, the remainder of this chapter assumes transfer to the ICU immediately postoperatively.

Once admitted to the ICU the initial assessment is similar to that performed after any major abdominal surgical procedure, with some additional considerations. The following aspects of care—some of which are discussed on more detail later—should be considered:

- *Respiratory status:* Initial assessment of the adequacy of oxygenation and ventilation is made by physical examination and by review of ventilator mechanics. The position of the tracheal tube should be assessed clinically and radiologically. Inadvertent extubation during transfer from the OR is very uncommon; advancement of the tube into the right mainstem during transfer is more likely. Both should be out-ruled. In addition to assessment of the position of the tracheal tube, a chest radiograph is used to evaluate the lung parenchyma and pleural cavities and assess the position of vascular access devices, the nasogastric tube, and chest tube if present. Intraoperatively a lung protective strategy should be used, with tidal volume adjusted for ideal body weight, and this strategy should be continued postoperatively. A high respiratory rate may be required to achieve adequate minute ventilation. It is important that, at least initially, the minute ventilation set on the ICU ventilator matches that delivered in the OR (assuming the most recent OR blood gases were satisfactory). A high minute ventilation may be required to compensate for a metabolic acidosis that commonly develops intraoperatively. Failure to recognize this and use of a “normal” minute ventilation in the early postoperative period may result in a rapidly-developing acidemia. Positive end-expiratory pressure (PEEP) is routinely used because LT recipients are prone to atelectasis and hypoxemia. PEEP should be titrated to improve oxygenation and prevent atelectrauma, while seeking to minimize increases in right atrial pressure that might compromise hepatic venous outflow (see below). Arterial blood gas analysis should be performed soon after the patient’s arrival in the ICU and mechanical ventilator support adjusted according to the results.
- *Neuromuscular blockade:* Non-depolarizing muscle relaxants are administered intraoperatively and neuromuscular blockade is usually still present on arrival in the ICU. The degree of residual neuromuscular blockade can be assessed with a peripheral nerve stimulator. Once an adequate train-of-four has been documented, reversal of neuromuscular blockade can be achieved by administration of neostigmine (with glycopyrrolate). Some intensivists wait for the drugs—typically atracurium or cisatracurium—to be metabolized and do not administer reversal agents. An adequate depth of sedation should be maintained while pharmacological paralysis is present.
- *Hemodynamics:* On transfer to the ICU, most recipients are relatively stable, albeit often on a low dose infusion of a vasoactive such as NE. Systolic blood pressures in the early post-operative period after an uncomplicated LT will be similar to pre-operative pressures, typically 90–120 mmHg, and reflective of the relatively low blood pressures seen in patients with end-stage liver disease. Soon after arrival to the ICU, as the patient warms, vasodilation and redistribution of intravascular volume (including sequestration of fluid into the operative field) occur and hypotension may ensue. This is typically treated with a mixture of crystalloid and colloid (usually albumin), and potentially with boluses of phenylephrine or ephedrine (depending on heart rate) and/or by titration of a vasopressor infusion. The PAC, if present, should be left in situ in the early postoperative period and—once temperature is adequate—should be used to measure cardiac index (CI) and pulmonary capillary wedge pressure (PCWP). These measurements should be used to calculate a full set of hemodynamic parameters. Thereafter, continuous display of central venous pressure (CVP) and pulmonary artery pressures (PAPs), coupled with assessment of CI and PCWP as required, may be used to follow the patient’s volume status and hemodynamic state. CVP is reflective of the outflow pressure for the liver and elevation may be associated with hepatic congestion. Intravascular volume depletion (which may, of course, represent ongoing bleeding) will tend to cause hypotension and tachycardia. This may be distinguished from vasodilation by measurement of systemic vascular resistance index (SVRI), which will be high in a volume-depleted state and low in vasodilation. The patient’s hemodynamics may fluctuate over the first few hours in the ICU and fluids and/or vasopressors may be required to



ensure adequate perfusion pressure. Left ventricular function may be compromised in patients with cirrhotic cardiomyopathy and NE is a good choice as it offers balanced alpha- and beta-adrenergic support and may be titrated with the goal of preservation of cardiac output and maintenance of afterload. Vasopressin may be added to decrease NE dose requirements. Mean arterial pressure of 65–70 mmHg is a reasonable target. If the liver allograft is very congested—indicated by high restive indices on postoperative Doppler ultrasound—a higher pressure target may be chosen.

- *Electrocardiogram (ECG):* A postoperative ECG should be performed routinely and compared with a preoperative ECG to evaluate for evidence of ischemia or electrolyte disturbance. It may be useful in the future as a postoperative baseline for comparison with subsequent ECGs should they be required.
- *Neurologic assessment:* Standard assessment of neurologic function may be supplemented by intracranial pressure (ICP) monitoring if an ICP monitor was placed pre-operatively.
- *Sedation:* Propofol is the agent typically used in the early postoperative period. The infusion initiated at the end of the procedure in the OR can be continued in the first hour postoperatively to allow for a quiescent period as the patient is assessed and routine postoperative cares and tests are performed. Doses of approx. 20–100 mcg/kg/min are typical and the dose is titrated to a Richmond Agitation Sedation Scale (RASS) score of –1 to –2, initially [22, 23]. Subsequently, propofol may be quickly weaned to allow for rapid emergence and extubation, assuming the patient is otherwise suitable. Dexmedetomidine is an alternative and the choice of agent may be clinician- and institution-dependent. Benzodiazepines should be avoided if possible, especially in patients with marginal graft function, in whom their metabolism may be delayed.
- *Analgesia:* Patients will have received a moderate dose of opiate intraoperatively, though often require additional analgesia early in the postoperative course. Bolus doses of fentanyl (nurse-controlled or patient-controlled) or a fentanyl infusion (0.25–2 mcg/kg/h) are good options. Longer acting agents such as hydromorphone may be chosen or required, though are not usually first choice. An adult behavioral pain scale, used to titrate sedative and analgesic medications based on hemodynamics and physical manifestations may also be used [24]. Many patients, especially if they have had preoperative encephalopathy, are sensitive to opiates and will require minimal or no additional analgesic medication postoperatively. Intravenous opiates, if used, are typically transitioned to oral weak opiates (e.g. oxycodone, tramadol), sometimes in combination with non-opiate analgesics such as acetaminophen, although the acetaminophen component should be omitted if graft function is questionable. Although LT recipients may have significant pain, their analgesic requirements are often less than the analgesic requirements for other upper abdominal procedures [25]. Ketamine is occasionally used in patients whose pain is difficult to treat, or in whom there is a pain-sedation mismatch. Although ketorolac is a very useful analgesic in the general surgical population, its use should be carefully considered in the LT recipient, especially with regard to its potential nephrotoxicity and effect on platelet function.
- *Abdominal evaluation:* The patient's abdomen should be clinically assessed for signs that might suggest ongoing bleeding. Physical examination, a subjective assessment, may be supplemented by measurement of abdominal girth, which will provide a potentially useful objective measure that may be compared serially. The volume, rate, and nature of abdominal deep drain output will help guide the need for transfusion of blood products or return to the OR for bleeding. Brisk drain output—sometimes at an alarmingly high rate—may indicate ongoing surgical bleeding, or a coagulopathy that requires urgent correction. If drain output stops, the drain may need to be manipulated or “stripped” to ensure that they have not clotted off. An external biliary drainage tube may be in situ; the production of golden-brown bile is a sign of allograft function.
- *Urine output:* Patients will have had an indwelling bladder catheter placed pre- or intra-operatively and hourly measurement of urine output should be recorded. Acceptable urine output is approximately 0.5 ml/kg/h, although in a well-resuscitated, hemodynamically stable patient it is often much greater. Oliguria is often of pre-renal origin, of which intravascular volume depletion is the most likely cause, although cardiac dysfunction should be considered. Pre-transplant renal dysfunction (see below) is relatively common, and urine output is one of a number of parameters used to decide upon initiation, continuation or cessation of dialysis. Polyuria is usually reflective of volume overload in a patient with intact renal function, the administration of furosemide, or may be secondary to cold-induced diuresis. Diabetes insipidus is an unlikely cause, though has been reported in the past in patients with acute liver failure who have suffered peri-transplant brain death.
- *Temperature management:* Perioperative hypothermia is well-recognized to be associated with adverse effects including coagulopathy, impaired wound healing, and myocardial dysfunction [26, 27]. Once neuromuscular blockade wears off, shivering may occur, with concomitant increase in oxygen consumption. Redistribution and evaporative heat loss induced by anesthesia and surgery and the use of ice and cold organ preservation solution

will tend to lower the patient's body temperature. Intraoperative hypothermia is common, despite use of forced-air warming blankets, airway gas humidifiers, and fluid warmers. Active warming is usually required on admission to the ICU. Methods of temperature optimization, with a goal of normothermia, include pre-warming of the ICU room, application of warm blankets and a forced-air warming device, and the use of fluid warmers.

- *Laboratory analyses:* Important laboratory analyses that should be performed early in the patient's ICU course include complete blood count, electrolytes, BUN and creatinine, INR, APTT, fibrinogen, thromboelastogram (TEG), and arterial blood gas analysis. These are usually performed as part of an institutional protocol (see below).
- *Interdisciplinary discussion:* Although the patient's medical record will provide much information regarding the patient's preoperative status, operative team members can provide further insight regarding the patient's condition on presentation to the OR. The ICU team should discuss the intraoperative events with the anesthesiologist and surgeon. Any difficulties with intubation or placement of vascular access should be noted. Details of the anesthetic management should include a discussion of the hemodynamic response to fluids or drugs and a description of the events around the time of allograft reperfusion. The surgeons can provide insight into the age of and nature of the donor (donation after brain death, DBD, or donation after cardiac death, DCD), the nature of the surgical dissection and anastomoses, organ ischemia time, and the appearance and initial function of the allograft.
- *Family discussion:* The perioperative period is a time of great stress for the patient's family and loved ones. The surgical team should discuss the intraoperative events with them. The critical care team may have already met family members because the recipient was in the ICU preoperatively. If not, in the early postoperative period, it is useful to have at least a brief introductory discussion to establish rapport, lessen anxiety and manage expectations.

### 20.3.1 Clinical Pathways and Protocols

The introduction of clinical pathways, protocols and "bundles" has occurred in an effort to standardize care, increase the adherence to evidence-based practices, and decrease errors of omission [28, 29]. The early postoperative care of the LT recipient is suitable for use of such care models. Ventilator management, ventilator weaning, and postoperative laboratory testing and imaging studies are but some

aspects of patient care that may be protocolized. Others include electrolyte replacement and glycemic control.

### 20.3.2 Function of the Liver Allograft

Of major influence on the postoperative course is the condition of the liver allograft. Adequate graft function will contribute significantly to stabilization of hemodynamics, resolution of metabolic acidosis, improvement in coagulopathy, and recovery of encephalopathy. High serum transaminase concentrations in the immediate postoperative period are typically due to reperfusion injury. (AST peaks first, usually within 24–48 h). Transaminases should fall during the first postoperative week. A cholestatic phase ensues and a bilirubin peak by 7–10 days is associated with a rise in alkaline phosphatase that can persist. If cholestasis is associated with worsening encephalopathy and coagulopathy this raises concern for graft failure. Bedside ultrasound of the hepatic allograft with Doppler examination of the hepatic artery and portal vein is usually performed immediately postoperatively and on the first postoperative day. In transplant centers, ultrasonographers and radiologists usually develop significant expertise in the performance and interpretation of postoperative hepatic ultrasound. They are thus able to differentiate expected postoperative findings from evidence of issues related to surgical technique and graft dysfunction. It may be possible to intervene and save the allograft if certain abnormalities are detected (e.g. portal vein or hepatic artery thrombosis).

The allograft suffers ischemic insults during procurement, preservation and implantation and these insults may cause "initial poor function". With appropriate cardiorespiratory and hemodynamic support this usually resolves over time, although treatment of coagulopathy and metabolic acidosis may be required during this period. The use of expanded criteria donors to increase the number of livers available for transplant has probably increased the incidence of initial poor function due to the transplantation of "marginal" allografts. Of greater concern is "primary non-function" an immunologic insult that is rare but extremely serious. The immunologic process begins in the OR after implantation of the graft and leads to graft failure requiring emergent retransplantation [30]. A non-functioning graft causes the development or persistence of metabolic acidosis, elevated lactate, increase in transaminases, worsening renal function, hyperkalemia, and hypoglycemia. Persistence or development of hepatic encephalopathy and signs of elevated intracranial pressure may also occur.

Acute cellular rejection may occur, although the routine use of tacrolimus for immunosuppression has decreased the risk. It is also less common in the elderly and the critically ill recipient [31]. Rejection should be considered if there is a

reversal in the trend of falling bilirubin or a sudden increase in serum transaminases at 5–10 days after LT.

It may be difficult to distinguish clinically or biochemically between vascular compromise, biliary disruption and rejection, and a further evaluation with Doppler ultrasonography, cholangiography or liver biopsy may be required.

## 20.4 System Based Considerations for Postoperative Management

### 20.4.1 Respiratory Considerations

Chapter 11 is dedicated to the pulmonary complications of liver disease. There are many reasons for hypoxemia in such patients and oxygenation may worsen in the perioperative period because of the induction of general anesthesia which causes atelectasis, and alterations in the mechanics of respiration caused by the upper abdominal surgical procedure.

Pleural effusions—hepatic hydrothoraces occur in up to 5% of patients with significant liver disease—may impair a patient's ability to wean from ventilatory support. If not drained intraoperatively, postoperative thoracentesis may be required [32]. Large volume ascites can also impair ventilation, although this is usually drained intraoperatively. Vital capacity may also be reduced by implantation of a new liver into the cavity previously occupied by a shrunken, cirrhotic liver. LT also results in disruption of diaphragmatic function.

#### 20.4.1.1 Liberation from Mechanical Ventilatory Support After “Routine” Liver Transplantation

The timing of extubation after LT has been debated [33, 34]. In “routine” cases LT recipients do not need prolonged mechanical ventilation and patients may be extubated within 6 h—often within 2 h. “Fast-tracking”, pioneered by the cardiac surgical community, is a process in which (among other things) short-acting medications are used intraoperatively to allow for rapid emergence from anesthesia and rapid weaning of ventilatory support [35, 36]. In appropriately selected patients a “fast track” or “rapid recovery” pathway has been demonstrated to be safe and to decrease costs. This concept has been embraced by the LT community and most transplant programs have developed protocols with prompt extubation as a goal. At Mayo Clinic the intraoperative use of midazolam, propofol, less than 20 mcg/kg of fentanyl, and intermediate –duration non-depolarizing muscle relaxants has been demonstrated to facilitate early ventilator weaning [15]. Early ventilator liberation may not decrease ICU length of stay, depending on ICU workflow and established protocols [15]. The definition of “prompt extubation” differs according to institution. (At the author's institution we aim

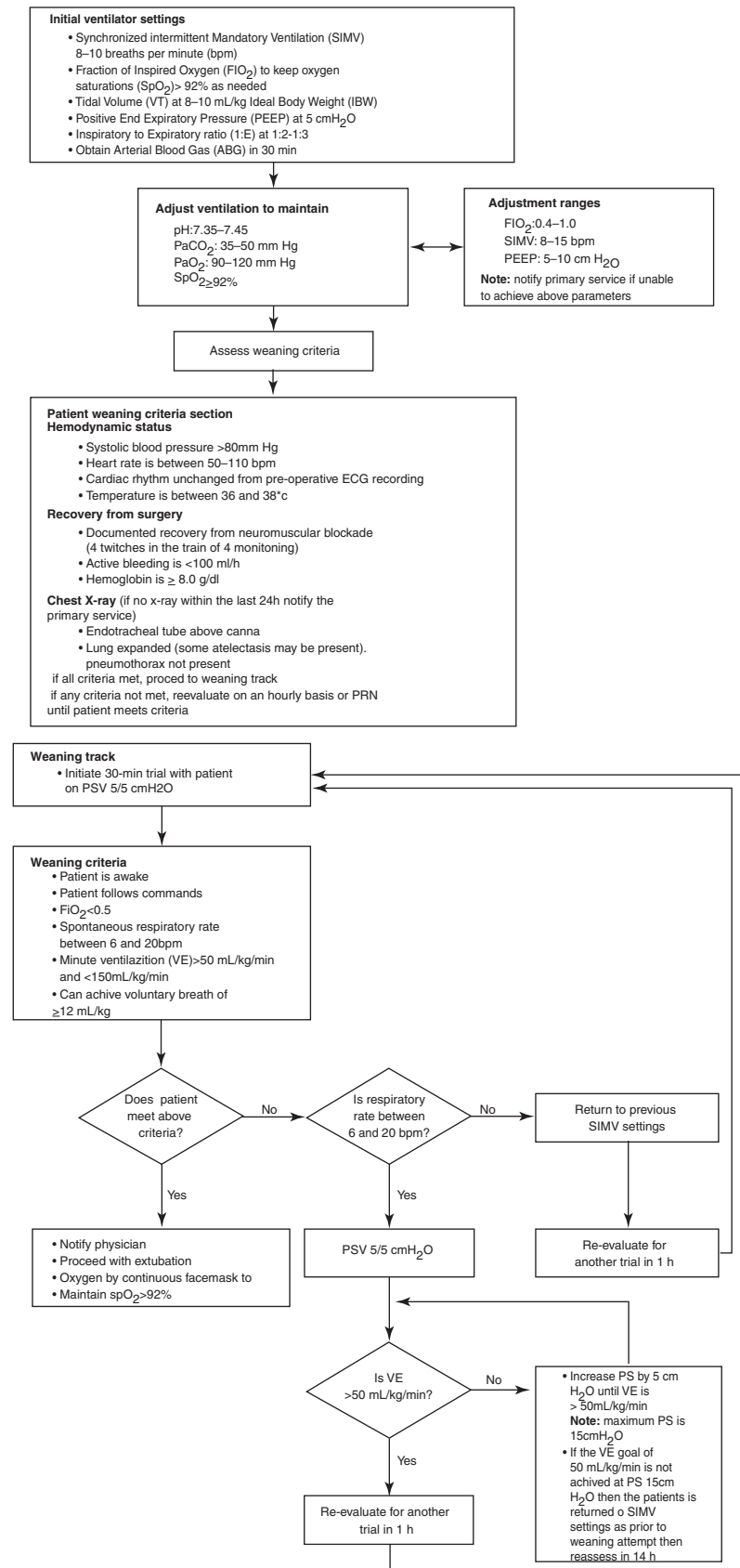
for extubation within two hours of the surgical procedure in suitable patients). Ventilator weaning protocols allow respiratory therapists and nurses to decrease sedation and ventilator support to the point of readiness for extubation (Fig. 20.1).

Immediate post-operative extubation has been advocated, based on a suggestion that early extubation might reduce the risk of ventilator associated pneumonia and provide beneficial effects on splanchnic and liver blood flow, might avoid ICU admission, and might decrease hospital length of stay and costs [37, 38]. Arguments against immediate postoperative extubation include the belief that a period of postoperative ventilation decreases the risks of aspiration, atelectasis, or reintubation for surgical exploration if necessary, and allows consolidation of graft function in a situation of decreased sympathetic stimulation [5, 34, 37]. Opponents argue that delaying extubation by a small number of hours allows assurance of hemodynamic stability, hemostasis and the presence of a functioning graft, and facilitates titration of narcotic analgesics for post-operative pain without compromising the patient's airway and respiratory status. At some centers, suitable patients are extubated in the OR and recovered in the post-anesthesia care unit (PACU) before transfer to a specialized surgical floor, thus “bypassing” the ICU [37–39]. The costs of PACU versus ICU stay intersect at about 6 h of PACU care and the level of nursing support in the PACU or the surgical floor is crucial [2]. Mandell et al. describe a cohort of 391 patients who received LTs at one of 7 centers (5 in the United States, 2 in Europe) who were extubated within one hour of completion of surgery [40]. Adverse events occurred in 7.7% of them within 72 h of surgery, although most of these adverse events were relatively minor. In some centers early extubation is performed in 60–70% of cases with avoidance of ICU admission in many of those cases, and reduction in costs [38, 41, 42]. A randomized trial of immediate versus early versus delayed extubation after LT has not yet been published.

#### 20.4.1.2 Patients in Whom Early Ventilator Liberation Is Not Possible

Many patients will not be suitable for early extubation after LT. As mentioned earlier, in the era of donor organ allocation according to MELD score, the acuity of LT recipients has increased and such patients may be unsuitable for “fast tracking”. Some may have required preoperative ventilation because of lung disease (e.g. alpha-1-antitrypsin deficiency, hepatopulmonary syndrome), severe malnourishment or preoperative sepsis. Diaphragmatic injury during the surgical procedure compounds the problem. Intraoperative difficulties leading to large volume transfusions, severe and persistent metabolic acidosis, ongoing bleeding and airway issues may delay extubation. Diuresis may be required prior to extubation in some patients. Inflammatory lung injury (see below) may develop in patients with liver failure, in those

**Fig. 20.1** Post-Liver transplant ventilator weaning protocol used at the author's institution. From Findlay JY, Keegan MT. Respiratory Failure and ARDS in Wagener G. Liver Anesthesiology and Critical Care. Springer, New York, 2012





who undergo complex abdominal surgery, and as a consequence of blood transfusion [43, 44]. Faenza and colleagues have identified the presence of early post-operative impairment of  $\text{PaO}_2/\text{FiO}_2$  as a predictor of prolonged post-operative ventilation [45]. In other patients, metabolism of citrate from administered packed red blood cells may lead to metabolic alkalosis and consequent hypoventilation, delaying extubation. Acetazolamide is occasionally required in such cases [46]. Pre-operative encephalopathy may result in delayed postoperative awakening, compromising the ability to extubate.

Yuan et al. reported data on 10,517 LT recipients transplanted between 2002 and 2008. Prolonged mechanical ventilation was associated with recipients who were older (age >50 years), female, who required pretransplant dialysis, or who had ascites [47]. When acute liver failure was the reason for LT, the presence of severe intraoperative hemodynamic derangements, advanced pre-operative encephalopathy, and renal dysfunction were predictors of prolonged postoperative ventilation [48].

LT recipients who require a longer duration of mechanical ventilation should be weaned according to published guidelines and recommendations [49, 50]. Recommendations include early consideration of weaning, use of spontaneous breathing trials to assess suitability for weaning, initial use of a 30-minute T-piece or low pressure support trial, pressure support or assist control mode for weaning, and use of non-invasive ventilation in selected patients [49, 51–56].

The need for tracheostomy is unusual in LT recipients [57]. If performed, it is usually delayed until two or three weeks of mechanical ventilation have been required. Percutaneous tracheostomy is increasingly used by the ICU community and there is some experience in transplant recipients [58, 59].

#### 20.4.1.3 Postoperative Pulmonary Edema

Pulmonary edema is common after LT. It has been reported by Golfieri et al. to occur in 45% of recipients, based on X-ray findings [60]. In the majority of cases the pulmonary edema was interstitial and associated with other signs of fluid overload and resolved with fluid restriction and diuretic use. Aduen et al. reported a prevalence of 52% in a series of 100 consecutive LTs [61]. Those patients in whom pulmonary edema was present immediately postoperatively and resolved within 24 h had outcomes similar to patients without pulmonary edema. In the patients with persistent pulmonary edema (18%) or in whom pulmonary edema developed in the postoperative period (9%) the duration of mechanical ventilation and ICU length of stay were increased. Persistent or late-onset pulmonary edema was associated with higher MELD score and was more likely to be related to altered capillary permeability rather than a hydrostatic mechanism.

#### 20.4.1.4 Acute Respiratory Distress Syndrome (ARDS) After LT

The surgical insult, reperfusion cytokine release, transfusion-related acute lung injury, sepsis, pre-operative (or less likely pre-induction) aspiration and treatment with monoclonal antibody therapy may cause acute respiratory distress syndrome (ARDS) in patients after LT [61–64]. Zhao et al. reported an incidence of ARDS (defined by the Berlin criteria) of 4.1% in 1726 adult patients who received LTs at a single center between 2004 and 2013 [65]. ARDS was associated with preoperative encephalopathy, the requirement for preoperative intubation, an elevation in serum bilirubin, and high intraoperative pressor requirements. The condition was associated with increases in the duration of mechanical ventilation, the duration of hospital stay, and mortality.

Patients with severe liver disease were excluded from the NIH-sponsored ARDSNet ARMA trial, the results of which demonstrated the advantage of a low tidal volume, lung-protective strategy [66]. It seems reasonable, however, to advocate for such a strategy in LT recipients who develop ARDS. The use of positive end expiratory pressure (PEEP), titrated to a level that exceeds pleural pressure, is an established method to improve oxygenation in mechanically ventilated patients and is especially useful in patients with ARDS [67, 68]. Although theoretically the application of PEEP may increase hepatic engorgement and compromise function of a new allograft, hepatic inflow and outflow are not impaired by PEEP levels up to about 15 cm  $\text{H}_2\text{O}$  [69–71]. The effects of higher PEEP levels are uncertain. There is minimal published experience with the use of permissive hypercapnia and high frequency oscillation in patients after LT. Reports of the use of prone positioning provide conflicting messages [72, 73]. Extra-corporeal membrane oxygenation (ECMO) is increasingly used as salvage therapy for patients with a variety of cardiac and respiratory conditions, including ARDS [74]. Park et al. described the use of venovenous ECMO in 18 adult LT recipients who developed postoperative respiratory failure (12 with pneumonia, 6 with ARDS) that was refractory to mechanical ventilation and concurrent inhaled nitric oxide. Eight of the patients survived [75].

#### 20.4.1.5 Use of Non-Invasive Ventilation in the Postoperative Period

Non-invasive ventilatory support (continuous positive airway pressure [CPAP] or biphasic positive airway pressure [BiPAP]) may be employed in the difficult-to-wean LT recipient who is not yet ready for complete withdrawal of mechanical ventilation but in whom extubation is desired [76]. It is also useful to avoid reintubation while a reversible problem (e.g. pulmonary edema due to volume overload, or opiate-induced hypoventilation) is treated [77]. The most common use of non-invasive ventilation in the postoperative LT

recipient, however, is probably the use of CPAP for the increasingly-recognized condition of obstructive sleep apnea.

#### **20.4.1.6 Ventilator-Associated Pneumonia (VAP)**

Although it is a major nosocomial problem and cause of ICU morbidity and mortality, VAP is unlikely to develop in the immediate postoperative period in LT recipients who are weaned quickly from the ventilator [78, 79]. In those who require longer durations of ventilator support the risk of VAP increases. Prevention, investigation and treatment should follow published guidelines [78, 80, 81]. Bronchoscopy and bronchoalveolar lavage (BAL) may be required to guide antimicrobial therapy. Consultation with a transplant infectious disease specialist should be considered if VAP develops.

#### **20.4.1.7 Hepatopulmonary Syndrome (HPS) in the Postoperative Period**

HPS is discussed in detail in Chap. 11. In the post-LT period, a failure of the  $\text{PaO}_2$  to adequately increase with administration of 100% oxygen may result in critical hypoxemia [82–84]. Weaning from mechanical ventilatory support may be challenging and, post-extubation, patients may require high-flow oxygen or non-invasive ventilator support that requires continued ICU care. Gupta et al. reported a median duration of post-LT ventilation of 1 day, but 23% of patients developed hypoxemic respiratory failure requiring ventilator support of up to 60 days [85]. Oxygen dependence may persist for weeks to months after extubation [86, 87]. Severe postoperative HPS-related hypoxemia may respond to Trendelenburg positioning or administration of intravenous methylene blue or inhaled N(G)-nitro-L-arginine methyl ester [88–90].

#### **20.4.1.8 Portopulmonary Hypertension (PPH) in the Postoperative Period**

As described in Chap. 9 patients with portopulmonary hypertension (PPH) are carefully screened and managed before LT is attempted [91–103]. Even with careful management, however, this group of patients represents a high perioperative risk cohort, because of the potential development of volume overload, metabolic or respiratory acidosis or hypoxemia, each of which will increase pulmonary artery pressures and potentially cause right ventricular failure at the time of reperfusion or early in the postoperative period. Patients are intolerant of large fluid shifts and massive hepatic and mesenteric congestion may occur. If low cardiac output develops graft ischemia and multiple organ failure may occur.

Pre-transplant therapy for PPH should be continued perioperatively and attempts to wean such therapies are best left until weeks after transplantation. It is imperative that in patients receiving continuous infusions of epoprostenol that the infusions continue without interruption as even a brief interruption may lead to rebound pulmonary hypertension. New onset or worsening right ventricular dysfunction and pulmonary hypertension may be treated with administration of inhaled nitric oxide, sildenafil or bosentan, or intravenous epoprostenol. In extreme circumstances, placement of a right ventricular assist device or performance of an atrial septostomy may be required [104–109].

### **20.4.2 Cardiac Considerations**

When patients are being assessed for suitability for LT screening for cardiac disease is an important element. The guidelines developed by the American College of Cardiology and the American Heart Association are widely used, but additional testing may also occur [110]. Resting and stress echocardiography are typically performed. The former provides information on baseline ventricular and valvular function and an estimate of the right ventricular systolic pressure to screen for pulmonary hypertension. Although some doubt has been cast on its utility in LT candidates, dobutamine stress echocardiography (DSE) is widely used for preoperative screening and seeks the presence of inducible ischemia that may warrant additional evaluation by a cardiologist [111–114].

Although this screening process means that only patients who have satisfactory cardiac function will be accepted as LT candidates, recipients may still have significant cardiac dysfunction that needs to be considered and managed perioperatively. As discussed in Chap. 9, patients with end-stage liver disease develop a vasodilation-associated hyperdynamic circulation. Atrial and right ventricular enlargement may be accompanied by diastolic dysfunction especially in patients with ascites, because of the increased effects of nitric oxide or endothelin-1 [115, 116]. The hyperdynamic circulation persists in the postoperative period and failure to see it might indicate hypovolemia, myocardial dysfunction, or a sinister cause [117]. After LT the vasodilated state will resolve over time. Restrictive cardiomyopathy may be present in patients who have undergone LT for hemochromatosis and this may blunt the usual hyperdynamic state.

Cardiac disease severity in the period after LT may be classified according to a system that assigns patients to one of four groups, depending on the presence and degree of hyperdynamic circulation, hyponatremia, portopulmonary

hypertension, cardiac dysfunction and malnutrition [116, 118]. Despite the apparently vigorous myocardium and the requirements for perioperative volume administration, patients with cirrhotic cardiomyopathy may develop intravascular overload relatively easily. Cautious administration of fluid is required in an effort to ensure adequate perfusion of the hepatic graft and other vital organs, but inotropic or vasoconstrictor support may also be required postoperatively. NE or epinephrine may be used, the former being more popular because of its powerful vasoconstrictor effect and concomitant inotropic properties, coupled with the fact that its associated tachycardia is usually not excessive. Dobutamine is occasionally used, but because of its “inodilator” properties, simultaneous use of a vasoconstrictor is often required. Vasopressin, a second line drug for restoration of blood pressure may be used as adjunctive therapy or as a catecholamine-sparing agent, though cost limits its use in some institutions. Vasopressin probably also decreases portal flow, however, with subsequent decrease in hepatic perfusion. Further details may be found in Chap. 9.

In a small number of patients, a decrease in left ventricular ejection fraction may occur, presenting a few days after the transplant procedure. This post-transplant dilated cardiomyopathy leads to pulmonary edema and respiratory failure, typically requiring readmission to ICU and initiation of invasive or non-invasive ventilatory support [119]. The condition is usually reversible with supportive treatment including diuresis and inotropic support. On occasion, apical ballooning suggests Takotsubo or stress-induced cardiomyopathy [120, 121].

Rarely, persistent postoperative hypotension may be caused by pericardial tamponade due to hemopericardium. This can occur because of injury to the parietal pericardium during placement of the superior aspect of the LT “Mercedes incision”, injury to the right atrium during performance of the superior vena cava anastomosis, or perforation of the superior vena cava or heart as a result of central venous catheter placement. Decreased cardiac output, high filling pressures, and a tendency to equalization of cardiac chamber pressures are typically seen, but profound vasodilation or hypovolemia may alter the hemodynamic profile. Diagnosis is made on clinical and echocardiographic grounds and treatment is by pericardiocentesis and/or surgical intervention.

In many LT programs serial troponin measurements are made postoperatively. Elevated levels were seen in 14 of 119 patients studied by Findlay et al., and may reflect intraoperative demand ischemia rather than significant coronary artery disease [113]. Ongoing postoperative myocardial ischemia is relatively unusual. Although heparin, anti-platelet agents, thrombolysis, and percutaneous coronary intervention are

less than ideal options in the postoperative period they should not immediately be ruled out. Discussions involving the surgeon, cardiologist, intensivist and the patient will usually lead to a satisfactory compromise.

#### 20.4.2.1 Postoperative Hypertension

In the postoperative period hypertension may be due to intolerance of the tracheal tube, incisional pain, anxiety, hypoglycemia, hypercapnia, volume overload and/or pre-existing chronic hypertension. If the systolic blood pressure is greater than 160 mmHg, intervention is probably required [122]. Intravenous agents such as labetalol or hydralazine are most useful early in the postoperative course. Once the period of “fluid-seeking” has resolved, longer-acting enteral agents may be used. Cyclosporine and tacrolimus activate the renin-angiotensin-aldosterone system and can lead to hypertension, although if it develops it usually occurs after ICU discharge. Postoperative pulmonary hypertension is covered in an earlier section.

#### 20.4.2.2 Postoperative Arrhythmias

Electrolyte imbalances (especially disorders of potassium, calcium, and magnesium), metabolic acidosis, hypoxemia and hypercapnia, volume overload or depletion, malpositioned central venous catheters, and myocardial ischemia may cause cardiac arrhythmias in the post-LT period. Atrial arrhythmias, especially atrial fibrillation, are relatively common as large fluid shifts and atrial distension occur [123]. Treatment of atrial fibrillation involves addressing the precipitating cause and achieving rate control with beta-blockers or calcium antagonists, measures that will often result in conversion to sinus rhythm. Amiodarone is not the ideal choice in patients after LT because of its potential hepatotoxicity, although it is usually effective in controlling rate and often effective in restoring sinus rhythm.

### 20.4.3 The Nervous System

As many as 25% of recipients have neurologic dysfunction in the perioperative period, the most common manifestations of which are encephalopathy and seizures [124–128].

The speed at which a patient awakens after LT is related to the rate of redistribution and metabolism of anesthetic and sedative agents and to the pre-operative mental status. The presence of pre-operative encephalopathy is associated with delayed postoperative awakening. Postoperative delirium is associated with worse outcomes in LT recipients [129]. As mentioned, the use of on short-acting agents and

low-moderate doses of analgesics as part of “fast-track” protocols allows awakening within 6 h in most cases—often much sooner.

Patients with acute liver failure (ALF) and cerebral edema should be managed differently to patients without this condition. Therapies initiated pre-operatively should be continued in the early postoperative period. Such interventions include minimization of noxious stimuli, avoidance of mechanical obstruction to cerebral venous outflow, mild hyperventilation, mannitol or hypertonic saline administration, use of the reverse Trendelenburg position, and potentially, moderate hypothermia [130–137]. Sedative weaning and awakening should be performed cautiously, guided by an intracranial pressure (ICP) monitor if there is one in situ, as the administration of sedative agents is one of the key management techniques for the treatment of cerebral edema. A functional liver allograft will eventually lead to a decrease in ICP, but there are rare reports of cerebral herniation intraoperatively and early postoperatively, leading to loss of the patient and the liver allograft.

Postoperative seizures are unusual. If they occur, intracranial hemorrhage or infarction, central nervous system infection, severe hyponatremia or hypocalcemia, and calcineurin inhibitor toxicity are the likely causes. Calcineurin inhibitors may also cause restlessness, tremor, and an acute confusional state.

Rapid increase in serum sodium in a patient with pre-existing hyponatremia may cause central pontine myelinolysis (CPM) because of changes in osmolality [126, 138]. Lee et al. documented CPM (or the similar condition, extrapontine myelinolysis) in 11 of 1247 patients (0.88%) who underwent LT between 1992 and 2005 [139]. A greater severity of preoperative liver dysfunction and larger changes in perioperative sodium concentration were associated with the condition. Awareness of the condition and a decrease in the use of sodium bicarbonate, coupled with an increase in the availability of non-sodium buffers such as tromethamine, has probably decreased the incidence of CPM [126, 138–141].

Psychological strain is common in patients after LT. The ICU Environmental Stressor Scale was used by Biancofiore and colleagues to evaluate recipients and they noted that insomnia, pain, the presence of tubes and drains, and limitations of family interaction were major stressors [142].

#### 20.4.4 Renal Considerations

Pre-LT renal dysfunction is common (as described in Chap. 20) but may also occur postoperatively. Hepatorenal syndrome (HRS) is only one of many potential causes, and is a diagnosis of exclusion, usually made pre-operatively. HRS generally recovers after LT unless irreversible damage has occurred. More common causes include intravascular volume depletion, acute tubular necrosis due to sepsis, and

nephrotoxins, as well as many primary renal etiologies [143–148]. If the renal dysfunction is long-enough established and deemed to be irreversible, a combined liver-kidney transplant may be performed.

Intraoperative hyperkalemia may be especially problematic in patients with renal dysfunction. Reperfusion of the hepatic allograft delivers a large potassium load to the systemic circulation and transfusion of multiple units of packed red blood cells is also associated with a potassium load. The presence of an acidemia will worsen the hyperkalemia. Potassium-depleted red cells may be available from the transfusion-medicine service and should be used in patients with severe renal dysfunction. Intraoperative hyperkalemia may persist into the postoperative period. If present, it may be treated with conventional measures to protect the heart, shift potassium from the plasma to the intracellular space, and decrease total body potassium. In mechanically ventilated patients, hyperventilation can be used in conjunction with administration of intravenous calcium (given until ECG abnormalities resolve) as initial measures to decrease serum potassium and preserve myocardial function. Administration of insulin with dextrose, beta-2 agonists, and sodium bicarbonate will also decrease potassium. Beta-2 agonists may improve or worsen cardiac arrhythmias that have developed in the setting of hyperkalemia. The severity of hyperkalemia must be considered in association with the presence or absence of hyponatremia when administration of sodium bicarbonate (which is usually readily available in the ICU) is being contemplated. Decreasing total body stores of potassium requires administration of furosemide (if the patient makes urine) or initiation of dialysis. Sodium polystyrene sulfonate may not be effective and has multiple associated complications.

In patients on intermittent hemodialysis, attempts should be made to optimize fluid and electrolyte status prior to LT, often by performing a hemodialysis run in the immediate pre-operative period. Some patients will have been in the ICU pre-operatively, and because of renal failure in the setting of hemodynamic instability, need continuous renal replacement therapy (CRRT) prior to LT. CRRT is usually not continued intraoperatively, though it is possible to do so to treat severe metabolic acidosis and hyperkalemia and to allow volume removal and decrease liver engorgement when a patient is anuric [149, 150]. Theoretically CRRT has advantages over intermittent HD for patients with elevated ICP and for those with portopulmonary hypertension.

Postoperatively, the need for re-initiation of dialysis should be assessed according to the usual criteria. One third of patients with pre-operative renal failure will require postoperative renal replacement therapy and 5% of those with pre-operative renal failure will need chronic dialysis.



New requirements for renal replacement therapy may develop postoperatively. Perioperative hypovolemia, hypotension, or cardiac dysfunction may cause azotemia, and renal injury may also result from acute tubular necrosis secondary to sepsis or an inflammatory state caused by the surgical procedure [151]. Post-operative hepatic allograft dysfunction may precipitate new post-operative renal dysfunction and nephrotoxic drugs especially immunosuppressants (e.g. tacrolimus) and antimicrobials (e.g. amphotericin) may also be responsible. Further, administration of large volumes of chloride-containing fluids may be associated with renal damage [152]. Optimization of hemodynamics and treatment of the underlying cause may allow renal recovery, with or without the need for renal replacement therapy. The absence of structural abnormality on renal biopsy correlates with recovery after liver-alone transplantation [153]. Biopsy is associated with potential morbidity, however, which limits its widespread application, especially in the early postoperative period.

## 20.4.5 Metabolic Considerations

### 20.4.5.1 Glycemic Control

There is a tendency to hyperglycemia in the LT recipient because of the surgical stress response, administration of steroids and exogenous catecholamines, and the insulin resistance associated with liver failure. Perioperative glycemic control and glycemic management in the critically ill have been subjects of much investigation [154–157]. Intraoperative glycemic control may affect graft function and post-operative complications in both liver and kidney transplant recipients, but the data are incomplete [158]. Hypoglycemia is a concern in patients with liver dysfunction and altered glycogen stores preoperatively, and in patients with marginal graft function postoperatively. The role of postoperative glycemic control in LT recipients is still uncertain, although there are some retrospective data [158–161].

Blood sugars between 100 and 139 mg/dl were targeted by Marvin and colleagues using a computer-based algorithm in the perioperative period in 32 LT recipients, though the study did not evaluate the implications of glycemic control [161]. A blood glucose target of 80–110 mg/dl was retrospectively compared with a target of less than 180 mg/dl [160]. Patients in the group with a lower target—despite achieving a target concentration only 24% of the time—demonstrated reduced infection and rejection rates, need for mechanical ventilation and requirement for blood transfusion. Whether these outcomes were causative or co-incidental is unclear. Ammori et al. retrospectively divided a cohort of 184 adult patients transplanted between 2004 and 2006 into those who achieved “strict” (mean intraoperative blood glucose <150 mg/dl) or “poor” (mean intraoperative glucose ≥150 mg/dl) [159]. The incidences of most post-operative

complications were similar, but poor glycemic control was associated with a significantly increased infection rate at 30 days post-transplantation and an increased 1-year mortality. In a large study of 680 LT recipients Park et al. demonstrated that an intraoperative glucose level > 200 mg/dl was associated, on multivariate analysis, with an increased risk of post-operative surgical site infection [162].

At Mayo Clinic, an insulin infusion is often initiated in the OR and continued into the postoperative period. ICU nurse-initiated and glycemic control protocols are also used. We have demonstrated adequate glycemic management with an excellent safety profile [163]. Sugars should be checked every hour when insulin infusions are being used and one needs to be especially careful to avoid hypoglycemia in patients with preoperative ALF and those with marginal graft function. Hypoglycemia should be treated with boluses of 50% dextrose, continuous infusions of 5% or 10% dextrose and adjustment of the insulin algorithms that may be in use.

### 20.4.5.2 Nutrition

Protein calorie malnutrition is common in advanced liver disease and is likely to worsen perioperatively because of the catabolic changes of the surgical stress response and the difficulty in achieving a positive protein balance in the immediate post-transplant period [164, 165]. Gastrointestinal function usually recovers quickly after an uncomplicated LT, so re-initiation of oral intake can occur within 24–48 h of surgery. At some centers, nasogastric or nasojejunal feeding is initiated postoperatively to preserve gut mucosal integrity and to provide caloric intake, though this is not the norm. Total parenteral nutrition is usually unnecessary and is less desirable than enteral feeding as it may be associated with steatotic hepatitis and central line associated blood stream infection.

### 20.4.5.3 Other Electrolyte and Metabolic Issues

In circumstances of large volume transfusion, citrate preservative in packed red blood cells may chelate enough calcium to cause hypocalcemia, which may impact hemodynamics and coagulation. Replacement should be by the intravenous route. Phosphate is required for liver parenchyma regeneration and hypophosphatemia should be anticipated and treated in patients who have undergone living donor liver transplantation (LDLT) or implantation of a split liver [166].

The concept of relative adrenal insufficiency in patients with sepsis has been the subject of research interest over the past decade [167, 168]. Given the finding of vasodilation in both sepsis and liver disease, Marik and colleagues evaluated adrenal function in patients with liver disease [169]. The large steroid bolus administered intraoperatively to patients undergoing LT provides adequate exogenous glucocorticoid levels, even if endogenous levels are insufficient. Relative adrenal insufficiency, may, however, occur months after LT [170].

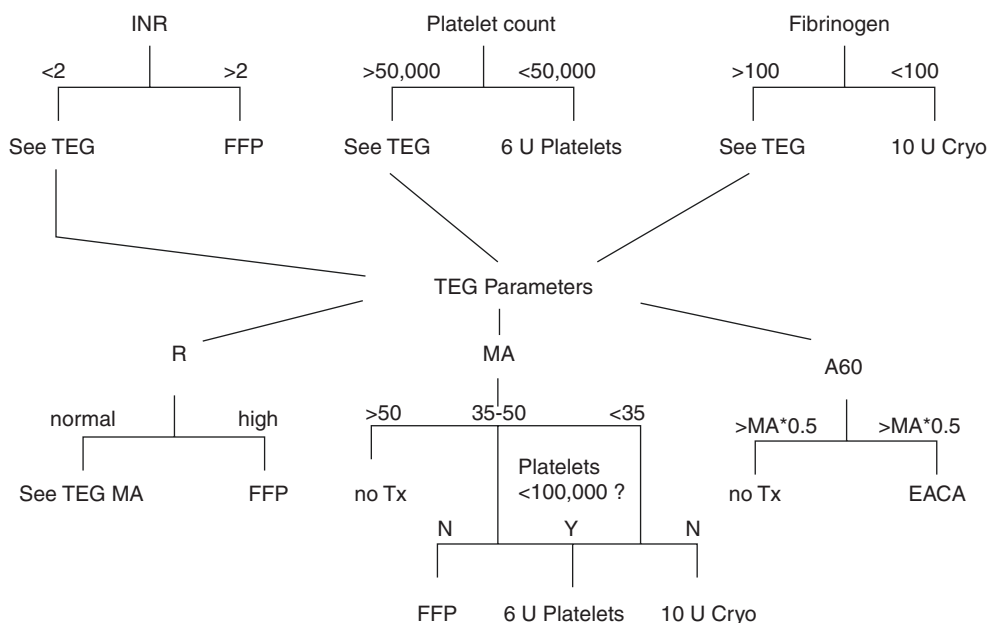
### 20.4.6 Coagulation Management

Derangements in the coagulation cascade that occur in patients with liver disease are detailed in Chap. 20 [171]. In the perioperative period the risk of bleeding must be weighed against the risk of hepatic artery or portal vein thrombosis. As the liver allograft starts to function, coagulation parameters will tend towards normalization. In the meantime, however, intra- and post-operative bleeding must be prevented and/or stopped. Thrombocytopenia is seen in virtually all recipients after transplantation, with lowest levels seen on the third and fourth postoperative days. In addition to conventional measures of coagulation such as INR, APTT, and platelet count, the TEG has been used extensively in the perioperative management of patients undergoing LT. Pioneered by liver transplant anesthesiologists for intraoperative management, the TEG is a whole blood coagulation test [172]. It is displayed as a graph that indicates coagulation over time. The TEG provides information regarding fibrin formation, fibrin-platelet plug construction and clot lysis by evaluating R time (from start of test to beginning of clot formation and corrected by administering fresh frozen plasma), K time (from start of clot until an amplitude of 20 mm, and impacted by fibrinogen), angle alpha (which measures the speed of fibrin build-up and is also impacted by fibrinogen), MA (maximum amplitude, which represents the ultimate strength of the fibrin clot, impacted by platelets) and MA + 30 and

MA + 60 which measure clot lysis at 30 and 60 min and are correctable by administration of aminocaproic acid. In the absence of worrisome bleeding, reasonable targets for coagulation tests include INR 1.5–2, fibrinogen > 50 mg/dl, and platelets >  $50 \times 10^9/L$ . A scheme for perioperative coagulation management is provided in Fig. 20.2.

### 20.4.7 Immunosuppression

The transplanted liver is less immunogenic than other solid organ allografts, but careful use of immunosuppression is key to graft and patient survival, and the development of more powerful immunosuppressive agents allowed the practice of LT to flourish. The first dose of immunosuppressant medication is usually administered in the OR. Different LT programs have specific recommendations, but a typical regimen includes corticosteroids, mycophenolate mofetil and a calcineurin inhibitor, either tacrolimus or cyclosporine. The large multi-person, multi-disciplinary team required to successfully care for a patient after LT, makes it essential to have clearly defined responsibilities for the prescription and administration of immunosuppressants. An ICU or transplant pharmacist is a valuable addition to the team. Dose omission and inappropriate dosing may compromise graft survival or cause toxicity to other organs. Both cyclosporine and tacrolimus can cause nephrotoxicity and neurotoxicity



**Fig. 20.2** Algorithm for the perioperative assessment and treatment of coagulation abnormalities in patients undergoing orthotopic liver transplantation. *FFP* Fresh frozen plasma, *Cryo* Cryoprecipitate, *TEG* Thromboelastogram, *R* TEG reaction time, *MA* TEG maximal amplitude, *A60* TEG amplitude 60 min after the time of MA,

*Tx* Treatment, *EACA* ε-aminocaproic acid. From Stapelfeldt W. Liver, Kidney, Pancreas Transplantation. In *Critical Care Medicine: Perioperative Management*, 2nd edition. Murray MJ, Coursin DB, Pearl RG, Prough DS eds. Lippincott Williams and Wilkins, Philadelphia, 2002. Page 728

[173–176]. Sirolimus has been associated with delayed wound healing and hepatic artery thrombosis in the perioperative period, but may be introduced later as a calcineurin-sparing agent. In patients with renal impairment, for whom use of a calcineurin inhibitor is suboptimal because of renal toxicity, thymoglobulin and IL-2 receptor antagonists may be used for induction of immunosuppression. Cytokine release caused by these agents may result in pulmonary edema and hemodynamic instability.

Unless primary non-function occurs, rejection is usually not seen during the first week after LT, so is usually not an ICU issue [173, 174, 176]. Early rejection, if it occurs, is more common in patients with pre-existing antibodies who have received an ABO incompatible donor graft or who have exhibited a strongly positive crossmatch. Rejection is uncommon in the elderly [31, 177]. The presenting features of rejection include increasing bilirubin, transaminases, and amylase, and, potentially, change in the character of the biliary output. Fever may or may not be present. Rejection may be confirmed by liver biopsy. Treatment is with high dose intravenous corticosteroids as a first line, with anti-lymphocyte therapy an option in non-responders.

## 20.4.8 Infectious Disease Issues

Prior to transplantation, LT candidates are prone to infection, including spontaneous bacterial peritonitis. Interaction with the healthcare system increases the risk for colonization with resistant organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Although infection is the leading cause of death in LT recipients, it is not the commonest cause in the immediate post-transplant period. Post-transplant infections may occur, however, given the frequency of pre-transplant patient debility, and such infections principally affect the lungs or abdominal cavity. Prophylaxis against surgical site infections is administered intraoperatively, usually with a third generation cephalosporin, but although bacterial infections predominate in the postoperative period, fungi such as *Candida* species or *Aspergillus* may cause early respiratory infections [178]. VAP is discussed earlier in this chapter. For a more detailed discussion of infectious disease considerations in patients with liver disease, the reader is referred to Chap. 15.

## 20.4.9 Postoperative Complications

### 20.4.9.1 Postoperative Hemorrhage

Approximately 10% of patients require reoperation within the first 24–48 h because of ongoing intra-abdominal bleeding [122, 179, 180]. Hypotension, abdominal distension, oliguria, elevated bladder (>20 cmH<sub>2</sub>O) and airway

(>40 cmH<sub>2</sub>O) pressures and failure of the hemoglobin to rise after transfusion are indicative signs. Intra-abdominal bleeding will usually manifest with brisk sanguinous deep abdominal drain output, but malfunctioning or clotted drains may hide the magnitude of bleeding. If there is a concern about significant intra-abdominal bleeding, coagulopathy should be fully corrected to decrease “medical” bleeding. There should be an ongoing dialog between members of the critical care and surgical teams to ensure that the patient is transferred back to the OR quickly when warranted. Re-exploration does not always identify a definite source of bleeding. Often, intra-abdominal clot is removed, the abdomen is washed out and the patient returned to the ICU. Identifiable sources of surgical bleeding include vascular anastomoses, the cystic bed, liver lacerations, and abdominal wall vessels. The presence of large, raw surfaces in recipients of LDLTs or split-liver grafts increases their risk of bleeding. Exploratory laparotomy in a patient who has abdominal bleeding has hemodynamic consequences. On the negative side, induction of anesthesia and release of the tamponading effect of intra-abdominal clot may cause hypotension and further bleeding. Often, however, difficulties with ventilation and hemodynamic compromise due to abdominal compartment syndrome will be ameliorated by opening the abdomen and addressing ongoing bleeding. Endovascular intervention to control post-transplant bleeding has been described but is not typical [181].

### 20.4.9.2 Vascular, Biliary, and Wound Complications

Between 6 and 12% of recipients develop vascular complications, though many of these will not manifest during the patient’s ICU stay [182]. Thrombosis is the most common complication, but arterial stenosis, pseudoaneurysm and dissection may occur. In the early postoperative period the risk of vessel thrombosis must be balanced against the risk of surgical site bleeding. The hepatic artery is a relatively small vessel. Postoperative hepatic artery thrombosis may present with marked elevation of transaminases and a rapid clinical deterioration. Ischemia of the bile duct, causing biliary leaks, may also occur because the biliary system obtains its blood supply from the hepatic artery. Retransplantation is required if hepatic necrosis develops. On occasion, an infusion of prostaglandin E1 (“alprostadil”), may be initiated if the surgical team are concerned about the quality and patency of the hepatic artery intraoperatively [183]. The drug is started at 40 mcg/kg/min increasing to a maximum of 160 mcg/kg/min, as tolerated by systemic blood pressure.

Thrombosis of the portal vein occurs less commonly. The clinical manifestations are variable, and include ascites, variceal bleeding and severe liver dysfunction. The critical care and surgical teams should be vigilant for the development of a vascular complication that compromises graft function, as

prompt return to the operating room for intervention may salvage the new liver.

Biliary complications occur in 6–34% of LT recipients. Patients who have received partial grafts are at higher risk. Bile leaks present with fever, abdominal pain, peritonitis, and bile in the drains. Surgical repair is often required. Biliary obstruction is usually not seen in the ICU in the early postoperative course. Although wound complications including infection and dehiscence are relatively common in LT recipients, they are not usually ICU problems.

## 20.4.10 Special Considerations

### 20.4.10.1 Acute Liver Failure

The management of a patient with acute liver failure (ALF) presents one of the greatest challenges to the intensivist. Chapters 8 and 21 provides a detailed discussion of the associated considerations. Consensus recommendations have been published to guide management [18, 184]. The perioperative care is fraught with difficulty. Multiple organ failure must be carefully managed by the anesthesiologist and intensivist, with particular attention paid to the control of intracranial pressure. LT recipients in the setting of ALF will remain extremely ill in the first postoperative days and, at least initially, will require continuation of therapies initiated preoperatively such as renal replacement therapy, vasoactive support, and intracranial pressure management.

### 20.4.10.2 Living Donor Liver Transplantation

In general, the ICU care of a recipient of a living donor LT is similar to that of a recipient who has received a cadaveric liver graft. The perioperative course may actually be smoother in the LDT recipient as the procedure—unless the recipient has ALF—is usually performed on an elective basis, allowing medical optimization of the recipient prior to transplant. Disadvantages also exist. The large raw liver surface present in LDLT recipients increases the risk of postoperative bleeding. Biliary complications are more common and the relatively small arterial anastomosis may lead to a higher incidence of thrombosis [185, 186].

In many programs the ICU team will also care for the liver donor on the night after surgery. A desire to minimize donor morbidity and to have zero donor mortality leads to routine ICU admission as an additional “safety margin” to ensure expertise is available for the immediate recognition and treatment of complications. Neuraxial techniques (epidural catheter or single injection spinal) are often used to provide postoperative analgesia in these patients who have usually undergone an extended right hepatectomy. Epidural analgesia has raised concerns because of post-operative coagulopathy in such patients and the risk, albeit very small, of epidural hematoma. Administration of intrathecal opiates

via a “single shot” technique is an attractive alternative, though this may lead to pruritus and/or delayed respiratory depression [187].

### 20.4.10.3 Use of Extended Criteria Donors and Donation After Cardiac Death

The need to increase the number of organs available for transplantation has led to the use of “marginal” or extended criteria donors. Furthermore, an initiative by the United Network for Organ Sharing in the United States, has led to the an increase in the number of organs procured after cardiac death [188]. Recipients of such organs may have a more difficult postoperative course because of initial poor function. It is essential—although it may be logistically difficult in certain circumstances—that the potential donor and potential recipient are cared for by different ICU teams.

## 20.5 Discharge from, and Readmission to, the ICU

Many LT recipients leave the ICU within 24 h of surgery. As discussed earlier, some may have not been admitted in the first place. Large bore central venous catheters are usually not required once the patient is ready for ICU discharge. They may be changed over a wire to a smaller bore central venous catheter or removed altogether. Peripherally inserted central catheters may be placed in recipients with inadequate peripheral venous access.

ICU readmission was required in 19% of 1200 LT recipients transplanted between 1984 and 1996 [189]. Readmission was associated with poorer graft outcome, increased morbidity, and increased costs. Cardiopulmonary deterioration led to most ICU readmissions in the Levy study and the reasons are similar today. Hypervolemia and decreased inspiratory capacity at the time of ICU discharge are associated with readmission [190]. Neurologic issues may also be responsible for a significant number of ICU readmissions after LT. Unsurprisingly, those who have had a prolonged ICU course or who were in the ICU pre-transplant have a higher risk of ICU readmission.

### Conclusion

LT is a major surgical procedure performed in patients who often have multiple organ system derangements. The perioperative care of the LT recipient has become “routine”. That does not mean that management of such patients is easy. A multidisciplinary approach and collaboration between the surgical and anesthesia teams and the critical care service is required to ensure a smooth transition from the OR to the ICU and subsequently to the surgical ward. The postoperative course is made smoother by the presence of a functioning liver allograft. Nonetheless,



careful management of cardiorespiratory support is required, coupled with the need for optimization of metabolic status and coagulopathy. The critical care team must be vigilant for the development of postoperative complications directly or indirectly related to the surgical procedure and be prepared to intervene quickly if required. New challenges are posed by the desire to decrease resource utilization while “pushing the envelope” in terms of patient acuity and organ suitability without losing focus on the maintenance of high quality outcomes.

## References

- Wiklund RA. Preoperative preparation of patients with advanced liver disease. *Crit Care Med*. 2004;32:S106–15.
- Hastie J, Moitra VK. Routine postoperative care after liver transplantation. In: Wagener G, editor. *Liver anesthesiology and critical care medicine*. New York: Springer; 2012.
- Humar A, Payne W. Critical care of liver and intestinal transplant recipients. In: Irwin R, Rippe J, editors. *Critical care medicine*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2008. p. 2133–49.
- Freeman RB Jr, Wiesner RH, Roberts JP, McDiarmid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. *Am J Transplant*. 2004;4(Suppl 9):114–31.
- Xia VW, Taniguchi M, Steadman RH. The changing face of patients presenting for liver transplantation. *Curr Opin Organ Transplant*. 2008;13:280–4.
- Findlay JY, Fix OK, Paugam-Burtz C, et al. Critical care of the end-stage liver disease patient awaiting liver transplantation. *Liver Transpl*. 2011;17:496–510.
- Knaak J, McVey M, Bazerbach F, et al. Liver transplantation in patients with end-stage liver disease requiring intensive care unit admission and intubation. *Liver Transpl*. 2015;21:761–7.
- Keegan MT, Plevak DJ. Critical care issues in liver transplantation. *Int Anesthesiol Clin*. 2006;44:1–16.
- Angus DC, Shorr AF, White A, Dremsizov TT, Schmitz RJ, Kelley MA. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med*. 2006;34:1016–24.
- Adhikari N, Sibbald W. The large cost of critical care: realities and challenges. *Anesth Analg*. 2003;96:311–4.
- Schumann R, Mandell MS, Mercaldo N, et al. Anesthesia for liver transplantation in United States academic centers: intraoperative practice. *J Clin Anesth*. 2013;25:542–50.
- Liu LL, Niemann CU. Intraoperative management of liver transplant patients. *Transplant Rev (Orlando)*. 2011;25:124–9.
- Hannaman MJ, Hevesi ZG. Anesthesia care for liver transplantation. *Transplant Rev (Orlando)*. 2011;25:36–43.
- Hall TH, Dhir A. Anesthesia for liver transplantation. *Semin Cardiothorac Vasc Anesth*. 2013;17:180–94.
- Findlay JY, Jankowski CJ, Vasdev GM, et al. Fast track anesthesia for liver transplantation reduces postoperative ventilation time but not intensive care unit stay. *Liver Transpl*. 2002;8:670–5.
- Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369:2525–34.
- Lee WM, Stravitz RT, Larson AM. Introduction to the revised American association for the study of liver diseases position paper on acute liver failure 2011. *Hepatology*. 2012;55:965–7.
- Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute liver failure study group. *Crit Care Med*. 2007;35:2498–508.
- Bernal W, Lee W, Wendon J, L'Arsen F, Williams R. Acute liver failure: a curable disease by 2024? *J Hepatol*. 2015;62:S112–20.
- Findlay JY, Long TR, Joyner MJ, Heimbach JK, Wass CT. Changes in transfusion practice over time in adult patients undergoing liver transplantation. *J Cardiothorac Vasc Anesth*. 2013;27:41–5.
- Ramsay M. Justification for routine intensive care after liver transplantation. *Liver Transpl*. 2013;19(Suppl 2):S1–5.
- Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the richmond agitation-sedation scale (RASS). *JAMA*. 2003;289:2983–91.
- Sessler CN, Gosnell MS, Grap MJ, et al. The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166:1338–44.
- Brown D, Whalen F, Keegan M, et al. Validation of a new adult behavior pain scale in surgical intensive care unit patients. *Crit Care Med*. 2006;34:A83.
- Eisenach JC, Plevak DJ, Van Dyke RA, et al. Comparison of analgesic requirements after liver transplantation and cholecystectomy. *Mayo Clin Proc*. 1989;64:356–9.
- Sessler DI. Perioperative heat balance. *Anesthesiology*. 2000;92:578–96.
- Sessler DI. Temperature monitoring and perioperative thermoregulation. *Anesthesiology*. 2008;109:318–38.
- Ely EW, Bennett PA, Bowton DL, Murphy SM, Florance AM, Haponik EF. Large scale implementation of a respiratory therapist-driven protocol for ventilator weaning. *Am J Respir Crit Care Med*. 1999;159:439–46.
- Todd SR, Sucher JF, Moore LJ, Turner KL, Hall JB, Moore FA. A multidisciplinary protocol improves electrolyte replacement and its effectiveness. *Am J Surg*. 2009;198:911–5.
- Brokelman W, Stel AL, Ploeg RJ. Risk factors for primary dysfunction after liver transplantation in the University of Wisconsin solution era. *Transplant Proc*. 1999;31:2087–90.
- Aduen JF, Sujay B, Dickson RC, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc*. 2009;84:973–8.
- Garcia N Jr, Mihai AA. Hepatic hydrothorax: pathophysiology, diagnosis, and management. *J Clin Gastroenterol*. 2004;38:52–8.
- Mandell MS, Campsen J, Zimmerman M, Biancospino G, Tsou MY. The clinical value of early extubation. *Curr Opin Organ Transplant*. 2009;14:297–302.
- Steadman RH. Con: immediate extubation for liver transplantation. *J Cardiothorac Vasc Anesth*. 2007;21:756–7.
- Myles PS, Daly DJ, Djaiani G, Lee A, Cheng DC. A systematic review of the safety and effectiveness of fast-track cardiac anesthesia. *Anesthesiology*. 2003;99:982–7.
- Campos JH. Fast track in thoracic anesthesia and surgery. *Curr Opin Anaesthesiol*. 2009;22:1–3.
- Ozier Y, Klinck JR. Anesthetic management of hepatic transplantation. *Curr Opin Anaesthesiol*. 2008;21:391–400.
- Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: patient attributes that determine early transfer to surgical wards. *Liver Transpl*. 2002;8:682–7.
- Taner CB, Willingham DL, Bulatao IG, et al. Is a mandatory intensive care unit stay needed after liver transplantation? Feasibility of fast-tracking to the surgical ward after liver transplantation. *Liver Transpl*. 2012;18:361–9.
- Mandell MS, Stoner TJ, Barnett R, et al. A multicenter evaluation of safety of early extubation in liver transplant recipients. *Liver Transpl*. 2007;13:1557–63.
- Biancospino G, Romanelli AM, Bindi ML, et al. Very early tracheal extubation without predetermined criteria in a liver transplant recipient population. *Liver Transpl*. 2001;7:777–82.

42. Glanemann M, Langrehr J, Kaisers U, et al. Postoperative tracheal extubation after orthotopic liver transplantation. *Acta Anaesthesiol Scand*. 2001;45:333–9.
43. Looney MR, Roubinian N, Gajic O, et al. Prospective study on the clinical course and outcomes in transfusion-related acute lung injury. *Crit Care Med*. 2014;42:1676–87.
44. Manez R, Kusne S, Martin M, et al. The impact of blood transfusion on the occurrence of pneumonitis in primary cytomegalovirus infection after liver transplantation. *Transfusion*. 1993;33:594–7.
45. Faenza S, Ravaglia MS, Cimatti M, Dante A, Spedicato S, Labate AM. Analysis of the causal factors of prolonged mechanical ventilation after orthotopic liver transplant. *Transplant Proc*. 2006;38:1131–4.
46. Carton EG, Plevak DJ, Kranner PW, Rettke SR, Geiger HJ, Coursin DB. Perioperative care of the liver transplant patient: part 2. *Anesth Analg*. 1994;78:382–99.
47. Yuan H, Tuttle-Newhall JE, Chawa V, et al. Prognostic impact of mechanical ventilation after liver transplantation: a national database study. *Am J Surg*. 2014;208:582–90.
48. Joshi D, O'Grady J, Patel A, et al. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. *Liver Int*. 2014;34:362–6.
49. MacIntyre N. Discontinuing mechanical ventilatory support. *Chest*. 2007;132:1049–56.
50. Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29:1033–56.
51. Burns KE, Adhikari NK, Keenan SP, Meade M. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. *BMJ*. 2009;338:b1574.
52. Brochard L, Thille AW. What is the proper approach to liberating the weak from mechanical ventilation? *Crit Care Med*. 2009;37:S410–5.
53. Epstein SK. Weaning from ventilatory support. *Curr Opin Crit Care*. 2009;15:36–43.
54. Mauri T, Pivi S, Bigatello LM. Prolonged mechanical ventilation after critical illness. *Minerva Anesthesiol*. 2008;74:297–301.
55. Girard TD, Ely EW. Protocol-driven ventilator weaning: reviewing the evidence. *Clin Chest Med*. 2008;29:241–52. v
56. Esteban A, Alia I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish lung failure collaborative group. *Am J Respir Crit Care Med*. 1999;159:512–8.
57. Frustos-Vivar F, Esteban A, Paezteguia C, Anzueto A, et al. Outcome of mechanically ventilated patients who require a tracheostomy. *Crit Care Med*. 2005;33:290–8.
58. Pirat A, Zeyneloglu P, Candan S, Akkuzu B, Arslan G. Percutaneous dilatational tracheotomy in solid-organ transplant recipients. *Transplant Proc*. 2004;36:221–3.
59. Waller EA, Aduen JF, Kramer DJ, et al. Safety of percutaneous dilatational tracheostomy with direct bronchoscopic guidance for solid organ allograft recipients. *Mayo Clin Proc*. 2007;82:1502–8.
60. Golfieri R, Giampalma E, Morselli Labate AM, et al. Pulmonary complications of liver transplantation: radiological appearance and statistical evaluation of risk factors in 300 cases. *Eur Radiol*. 2000;10:1169–83.
61. Aduen JF, Stapelfeldt WH, Johnson MM, et al. Clinical relevance of time of onset, duration, and type of pulmonary edema after liver transplantation. *Liver Transpl*. 2003;9:764–71.
62. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–33.
63. Yost CS, Matthay MA, Gropper MA. Etiology of acute pulmonary edema during liver transplantation : a series of cases with analysis of the edema fluid. *Chest*. 2001;119:219–23.
64. Sachdeva A, Matuschak GM. Diffuse alveolar hemorrhage following alemtuzumab. *Chest*. 2008;133:1476–8.
65. Zhao W, Ge X, Sun K, et al. Acute respiratory distress syndrome after orthotopic liver transplantation. *J Crit Care*. 2016;31:163–7.
66. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–8.
67. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:327–36.
68. Villar J, Kacmarek R, Perez-Mendez L, Aguirre-Jaime A. A high positive-end expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized control trial. *Crit Care Med*. 2006;34:1311–8.
69. Saner FH, Damink SW, Pavlakovic G, et al. Is positive end-expiratory pressure suitable for liver recipients with a rescue organ offer? *J Crit Care*. 2009;25(3):477–82.
70. Saner FH, Olde Damink SW, Pavlakovic G, et al. Positive end-expiratory pressure induces liver congestion in living donor liver transplant patients: myth or fact. *Transplantation*. 2008;85:1863–6.
71. Saner FH, Pavlakovic G, Gu Y, et al. Effects of positive end-expiratory pressure on systemic haemodynamics, with special interest to central venous and common iliac venous pressure in liver transplanted patients. *Eur J Anaesthesiol*. 2006;23:766–71.
72. Sykes E, Cosgrove JF, Nesbitt ID, O'Suilleabhain CB. Early non-cardiogenic pulmonary edema and the use of PEEP and prone ventilation after emergency liver transplantation. *Liver Transpl*. 2007;13:459–62.
73. De Schryver N, Castanares-Zapatero D, Laterre PF, Wittebole X. Prone positioning induced hepatic necrosis after liver transplantation. *Intensive Care Med*. 2015;41(10):1833.
74. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365:1905–14.
75. Park YH, Hwang S, Park HW, et al. Effect of pulmonary support using extracorporeal membrane oxygenation for adult liver transplant recipients with respiratory failure. *Transplant Proc*. 2012;44:757–61.
76. Ferrer M. Non-invasive ventilation as a weaning tool. *Minerva Anesthesiol*. 2005;71:243–7.
77. Antonelli M, Conti G, Bui M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283:235–41.
78. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867–903.
79. Hunter JD. Ventilator associated pneumonia. *BMJ*. 2012;344:e3325.
80. Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305–13.
81. Coffin SE, Klompas M, Classen D, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008;29(Suppl 1):S31–40.
82. Koch DG, Fallon MB. Hepatopulmonary syndrome. *Clin Liver Dis*. 2014;18:407–20.
83. Fauconnet P, Klopfenstein CE, Schiffer E. Hepatopulmonary syndrome: the anaesthetic considerations. *Eur J Anaesthesiol*. 2013;30:721–30.
84. Hoepfer MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet*. 2004;363:1461–8.
85. Gupta S, Castel H, Rao RV, et al. Improved survival after liver transplantation in patients with hepatopulmonary syndrome. *Am J Transplant*. 2010;10:354–63.

86. Collisson EA, Nourmand H, Fraiman MH, et al. Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl.* 2002;8:925–31.
87. Taille C, Cadranet J, Bellocq A, et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation.* 2003;75:1482–9. discussion 46–7.
88. Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med.* 2000;133:701–6.
89. Brussino L, Bucca C, Morello M, Scappaticci E, Mauro M, Rolla G. Effect on dyspnoea and hypoxaemia of inhaled N(G)-nitro-L-arginine methyl ester in hepatopulmonary syndrome. *Lancet.* 2003;362:43–4.
90. Roma J, Balbi E, Pacheco-Moreira L, et al. Methylene blue used as a bridge to liver transplantation postoperative recovery: a case report. *Transplant Proc.* 2010;42:601–4.
91. Nayak RP, Li D, Matuschak GM. Portopulmonary hypertension. *Curr Gastroenterol Rep.* 2009;11:56–63.
92. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl.* 2000;6:443–50.
93. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med.* 2006;173:1023–30.
94. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: results from a 10-year screening algorithm. *Hepatology.* 2006;44:1502–10.
95. Swanson KL, Wiesner RH, Nyberg SL, Rosen CB, Krowka MJ. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. *Am J Transplant.* 2008;8:2445–53.
96. Kawut SM, Krowka MJ, Trotter JF, et al. Clinical risk factors for portopulmonary hypertension. *Hepatology.* 2008;48:196–203.
97. Cartin-Ceba R, Krowka MJ. Portopulmonary hypertension. *Clin Liver Dis.* 2014;18:421–38.
98. Kim BJ, Lee SC, Park SW, et al. Characteristics and prevalence of intrapulmonary shunt detected by contrast echocardiography with harmonic imaging in liver transplant candidates. *Am J Cardiol.* 2004;94:525–8.
99. Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl.* 2000;6:453–8.
100. Krowka MJ, Mandell MS, Ramsay MA, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl.* 2004;10:174–82.
101. Hoepfer MM, Gall H, Seyfarth HJ, et al. Long-term outcome with intravenous iloprost in pulmonary arterial hypertension. *Eur Respir J.* 2009;34:132–7.
102. Sussman N, Kaza V, Barshes N, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. *Am J Transplant.* 2006;6:2177–82.
103. Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. *Am J Transplant.* 2007;7:1258–64.
104. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;42:158–64.
105. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119–23.
106. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation.* 1997;63:604–6.
107. Ramsay M. Portopulmonary hypertension and right heart failure in patients with cirrhosis. *Curr Opin Anaesthesiol.* 2010;23:145–50.
108. Ramsay MA, Spikes C, East CA, et al. The perioperative management of portopulmonary hypertension with nitric oxide and epoprostenol. *Anesthesiology.* 1999;90:299–301.
109. Findlay JY, Harrison BA, Plevak DJ, Krowka MJ. Inhaled nitric oxide reduces pulmonary artery pressures in portopulmonary hypertension. *Liver Transpl Surg.* 1999;5:381–7.
110. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation.* 2014;130:2215–45.
111. Plotkin JS, Benitez RM, Kuo PC, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. *Liver Transpl Surg.* 1998;4:253–7.
112. Williams K, Lewis JF, Davis G, Geiser EA. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. *Transplantation.* 2000;69:2354–6.
113. Findlay JY, Keegan MT, Pellikka PP, Rosen CB, Plevak DJ. Preoperative dobutamine stress echocardiography, intraoperative events, and intraoperative myocardial injury in liver transplantation. *Transplant Proc.* 2005;37:2209–13.
114. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc.* 2008;40:3554–7.
115. Valeriano V, Funaro S, Lionetti R, et al. Modification of cardiac function in cirrhotic patients with and without ascites. *Am J Gastro.* 2000;95:3200–5.
116. McGilvray ID, Greig PD. Critical care of the liver transplant patient: an update. *Curr Opin Crit Care.* 2002;8:178–82.
117. Nasraway SA, Klein RD, Spanier TB, Rohrer RJ, Freeman RB, Rand WM, Benotti PN. Hemodynamic correlates of outcome in patients undergoing orthotopic liver transplantation. Evidence for early postoperative myocardial depression. *Chest.* 1995;107:218–24.
118. Lowell J, Shaw B. Critical care of liver transplant recipients. In: Maddrey W, Schiff E, Sorrell M, editors. *Transplantation of the liver.* Philadelphia: Lippincott Williams and Williams; 2001. p. 385–404.
119. Sampathkumar P, Lerman A, Kim BY, et al. Post-liver transplantation myocardial dysfunction. *Liver Transpl Surg.* 1998;4:399–403.
120. Adar T, Chen S, Mizrahi M. A heartbreaking case of Wilson's disease: Takotsubo cardiomyopathy complicating fulminant hepatic failure. *Transpl Int.* 2014;27:e109–11.
121. Harika R, Bermas K, Hughes C, Al-Khafaji A, Iyer M, Wallace DJ. Cardiac arrest after liver transplantation in a patient with takotsubo cardiomyopathy. *BJA.* 2014;112:594–5.
122. Plevak DJ, Southorn PA, Narr BJ, Peters SG. Intensive-care unit experience in the Mayo liver transplantation program: the first 100 cases. *Mayo Clin Proc.* 1989;64:433–45.
123. Xia VW, Worapot A, Huang S, et al. Postoperative atrial fibrillation in liver transplantation. *Am J Transpl.* 2015;15:687–94.
124. Fu KA, DiNorcia J, Sher L, et al. Predictive factors of neurological complications and one-month mortality after liver transplantation. *Front Neurol.* 2014;5:275.
125. Saner F, Gu Y, Minouchehr S, et al. Neurological complications after cadaveric and living donor liver transplantation. *J Neurol.* 2006;253:612–7.
126. Ardizzone G, Arrigo A, Schellino M, et al. Neurological complications of liver cirrhosis and orthotopic liver transplant. *Transplant Proc.* 2006;38:789–92.



127. Wijdicks EF. Impaired consciousness after liver transplantation. *Liver Transpl Surg.* 1995;1:329–34.
128. Zivkovic SA. Neurologic complications after liver transplantation. *World J Hepatol.* 2013;5:409–16.
129. Lescot T, Karvellas CJ, Chaudhury P, et al. Postoperative delirium in the intensive care unit predicts worse outcomes in liver transplant recipients. *Can J Gastro.* 2013;27:207–12.
130. Wijdicks EF, Nyberg SL. Propofol to control intracranial pressure in fulminant hepatic failure. *Transplant Proc.* 2002;34:1220–2.
131. Wijdicks EFMPD, Rakela J, et al. Clinical and radiologic features of cerebral edema in fulminant hepatic failure. *Mayo Clin Proc.* 1995;70:119–24.
132. Wijdicks EF. The diagnosis of brain death. *N Engl J Med.* 2001;344:1215–21.
133. Dmello D, Cruz-Flores S, Matuschak GM. Moderate hypothermia with intracranial pressure monitoring as a therapeutic paradigm for the management of acute liver failure: a systematic review. *Intensive Care Med.* 2010;36:210–3.
134. Stravitz RT, Larsen FS. Therapeutic hypothermia for acute liver failure. *Crit Care Med.* 2009;37:S258–64.
135. Daas M, Plevak DJ, Wijdicks EF, et al. Acute liver failure: results of a 5-year clinical protocol. *Liver Transpl Surg.* 1995;1:210–9.
136. Jalan R, O Damink SW, Deutz NE, Lee A, Hayes PC. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet.* 1999;354:1164–8.
137. Jalan R, Olde Damink SW, Deutz NE, et al. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. *Transplantation.* 2003;75:2034–9.
138. Wijdicks EF, Blue PR, Steers JL, Wiesner RH. Central pontine myelinolysis with stupor alone after orthotopic liver transplantation. *Liver Transpl Surg.* 1996;2:14–6.
139. Lee EM, Kang JK, Yun SC, et al. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. *Eur Neurol.* 2009;62:362–8.
140. Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients—incidence, timing, and long-term follow-up. *Clin Transpl.* 2000;14:1–7.
141. Hudcova J, Ruthazer R, Bonney I, Schumann R. Sodium homeostasis during liver transplantation and correlation with outcomes. *Anesth Analg.* 2014;119:1420–8.
142. Biancofiore G, Bindi ML, Romanelli AM, Urbani L, Mosca F, Filippini F. Stress-inducing factors in ICUs: what liver transplant recipients experience and what caregivers perceive. *Liver Transpl.* 2005;11:967–72.
143. Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. *Lancet.* 2003;362:1819–27.
144. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. *Crit Care.* 2004;8:R204–12.
145. Lebron Gallardo M, Herrera Gutierrez ME, Seller Perez G, Curiel Balsera E, Fernandez Ortega JF, Quesada GG. Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transpl.* 2004;10:1379–85.
146. Cabazuelo J, Ramirez P, Rios A, et al. Risk factors of acute renal failure after liver transplantation. *Kidney Int.* 2006;69:1073–80.
147. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med.* 1999;341:403–9.
148. Mulkay JP, Louis H, Donckier V, et al. Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: a pilot study. *Acta Gastroenterol Belg.* 2001;64:15–9.
149. Gali B, Keegan M, Leung N, Findlay J, Plevak D. Continuous renal replacement therapy during high risk liver transplantation. *Liver Transpl.* 2006;12:C-117.
150. Townsend DR, Bagshaw SM, Jacka MJ, Bigam D, Cave D, Gibney RT. Intraoperative renal support during liver transplantation. *Liver Transpl.* 2009;15:73–8.
151. Cabezuelo JB, Ramirez P, Rios A, et al. Risk factors of acute renal failure after liver transplantation. *Kidney Int.* 2006;69:1073–80.
152. Nadeem A, Salahuddin N, El Hazmi A, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. *Crit Care.* 2014;18:625.
153. Wadei HM, Geiger XJ, Cortese C, et al. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. *Am J Transpl.* 2008;8:2618–26.
154. Akhtar S, Barash PG, Inzucchi SE. Scientific principles and clinical implications of perioperative glucose regulation and control. *Anesth Analg.* 2010;110:478–97.
155. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283–97.
156. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* 2009;180:821–7.
157. Moghissi E, Korytkowski M, DiNardo M, et al. American association of clinical endocrinologists and American diabetes association consensus statement on inpatient glycemic control. *Endocr Pract.* 2009;15:353–69.
158. Marvin M, Morton V. Glycemic control and organ transplantation. *J Diabetes Sci Technol.* 2009;3:1365–72.
159. Ammori JB, Sigakis M, Englesbe MJ, O'Reilly M, Pelletier SJ. Effect of intraoperative hyperglycemia during liver transplantation. *J Surg Res.* 2007;140:227–33.
160. Hsaiky L, Bajjoka I, Patel D, Abouljoud M. Postoperative use of intense insulin therapy in liver transplant recipients. *Am J Transplant.* 2008;8(S2):260.
161. Marvin M, Rocca J, Farrington E, et al. Intensive perioperative insulin therapy in liver transplant patients—effective implementation with a computer-based dosage calculator. *Am J Transplant.* 2006;6(S2):986.
162. Park C, Hsu C, Neelakanta G, et al. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. *Transplantation.* 2009;87:1031–6.
163. Keegan MT, Vrchota JM, Haala PM, Timm JV. Safety and effectiveness of intensive insulin protocol use in post-operative liver transplant recipients. *Transplant Proc.* 2010;42:2617–24.
164. Stephenson GR, Moretti EW, El-Moalem H, Clavien PA, Tuttle-Newhall JE. Malnutrition in liver transplant patients: preoperative subjective global assessment is predictive of outcome after liver transplantation. *Transplantation.* 2001;72:666–70.
165. Nompleggi DJ, Bonkovsky HL. Nutritional supplementation in chronic liver disease: an analytical review. *Hepatology.* 1994;19:518–33.
166. Pomposelli JJ, Pomfret EA, Burns DL, et al. Life-threatening hypophosphatemia after right hepatic lobectomy for live donor adult liver transplantation. *Liver Transpl.* 2001;7:637–42.
167. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862–71.
168. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008;358:111–24.
169. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med.* 2006;32:275–80.
170. Iwasaki T, Tominaga M, Fukumoto T, et al. Relative adrenal insufficiency manifested with multiple organ dysfunction in a liver transplant patient. *Liver Transpl.* 2006;12:1896–9.



171. Barton CA. Treatment of coagulopathy related to hepatic insufficiency. *Crit Care Med*. 2016;44:1927–33.
172. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (N Y)*. 2012;8:513–20.
173. Cohen SM. Current immunosuppression in liver transplantation. *Am J Ther*. 2002;9:119–25.
174. Buckley RH. Transplantation immunology: organ and bone marrow. *J Allergy Clin Immunol*. 2003;111:S733–44.
175. Wijdicks EF. Neurotoxicity of immunosuppressive drugs. *Liver Transpl*. 2001;7:937–42.
176. Textor SC, Taler SJ, Canzanello VJ, Schwartz L, Augustine JE. Posttransplantation hypertension related to calcineurin inhibitors. *Liver Transpl*. 2000;6:521–30.
177. Manez R, Kusne S, Linden P, et al. Temporary withdrawal of immunosuppression for life-threatening infections after liver transplantation. *Transplantation*. 1994;57:149–51.
178. Aduen JF, Hellinger WC, Kramer DJ, et al. Spectrum of pneumonia in the current era of liver transplantation and its effect on survival. *Mayo Clin Proc*. 2005;80:1303–6.
179. Liang TB, Bai XL, Li DL, Li JJ, Zheng SS. Early postoperative hemorrhage requiring urgent surgical reintervention after orthotopic liver transplantation. *Transplant Proc*. 2007;39:1549–53.
180. Biancofiore G, Bindi ML, Romanelli AM, et al. Intra-abdominal pressure monitoring in liver transplant recipients: a prospective study. *Intensive Care Med*. 2003;29:30–6.
181. Harman A, Boyvat F, Hasdogan B, Aytekin C, Karakayali H, Haberal M. Endovascular treatment of active bleeding after liver transplant. *Exp Clin Transplant*. 2007;5:596–600.
182. Cavallari A, Vivarelli M, Bellusci R, Jovine E, Mazziotti A, Rossi C. Treatment of vascular complications following liver transplantation: multidisciplinary approach. *Hepato-Gastroenterology*. 2001;48:179–83.
183. Gatta A, Dante A, Del Gaudio M, et al. The use of prostaglandins in the immediate postsurgical liver transplant period. *Transplant Proc*. 2006;38:1092–5.
184. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179–97.
185. Liu LU, Schiano TD. Adult live donor liver transplantation. *Clin Liver Dis*. 2005;9:767–86.
186. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med*. 2002;346:1074–82.
187. Borromeo CJ, Stix MS, Lally A, Pomfret EA. Epidural catheter and increased prothrombin time after right lobe hepatectomy for living donor transplantation. *Anesth Analg*. 2000;91:1139–41.
188. Bernat JL, D'Alessandro AM, Port FK, et al. Report of a national conference on donation after cardiac death. *Am J Transpl*. 2006;6:281–91.
189. Levy MF, Greene L, Ramsay MA, et al. Readmission to the intensive care unit after liver transplantation. *Crit Care Med*. 2001;29:18–24.
190. Cardoso FS, Karvellas CJ, Kneteman NM, Meeberg G, Fidalgo P, Bagshaw SM. Respiratory rate at intensive care unit discharge after liver transplant is an independent risk factor for intensive care unit readmission within the same hospital stay: a nested case-control study. *J Crit Care*. 2014;29:791–6.

# Use of Extra-Corporeal Liver Support Therapies in Acute and Acute on Chronic Liver Failure

21

Constantine J. Karvellas, Jody C. Olson,  
and Ram M. Subramanian

## Abstract

Artificial (non-biological) extracorporeal liver support (ECLS) devices aim to remove albumin-bound and water soluble toxins in order to restore and preserve hepatic function and mitigate or limit the progression of multiorgan failure while either hepatic recovery or liver transplant occurs. Current artificial ECLS devices differ primarily in selectivity of the membrane utilized; dialysis based techniques such as the molecular adsorbent recirculating system (MARS®) combine renal replacement therapy with albumin dialysis and a highly selective (<50 kDa) filter in contrast to plasmapheresis (HVP)/plasma separation and filtration (Prometheus) techniques which are less selective (~250 kDa). Artificial ECLS devices have been used to support patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). These devices have been shown to be safe. The following beneficial effects have been documented: improvement of jaundice, amelioration of haemodynamic instability, reduction of portal hypertension, and improvement of hepatic encephalopathy. However, the only randomized prospective multicenter controlled trial to show an improvement in transplant-free survival was for HVP. Biological (cell based) extracorporeal liver support systems (B-ECLS) aim to support the failing liver both through detoxification and synthetic function and warrant further study for safety and benefit.

## Keywords

Extracorporeal liver support • Albumin dialysis • Acute liver failure • Acute-on-chronic liver failure • Extracorporeal liver assist device • Liver transplantation

C.J. Karvellas, M.D., S.M., F.R.C.P.C. (✉)  
Department of Critical Care Medicine, University of Alberta,  
Edmonton, AB, Canada

Division of Gastroenterology (Liver Unit), Division of Critical  
Care Medicine, University of Alberta,  
1-40 Zeidler Leducor Building, Edmonton, AB T6G-2X8, Canada  
e-mail: [dean.karvellas@ualberta.ca](mailto:dean.karvellas@ualberta.ca)

J.C. Olson, M.D.  
Division of Hepatology, University of Kansas,  
Kansas City, MO, USA

Division of Critical Care Medicine, University of Kansas,  
Kansas City, MO, USA  
e-mail: [jolson2@kumc.edu](mailto:jolson2@kumc.edu)

R.M. Subramanian, M.D.  
Division of Hepatology, Emory University, Atlanta, GA, USA

Division of Critical Care Medicine, Emory University,  
Atlanta, GA, USA  
e-mail: [rmsubra@emory.edu](mailto:rmsubra@emory.edu)

## Abbreviations

ACLF	Acute on chronic liver failure
ALF	Acute liver failure
ECLS	Extracorporeal liver support
FPSCA	Fractionated plasma separation and adsorption
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
INR	International normalised ratio
LT	Liver transplantation
MAP	Mean arterial pressure
MARS®	Molecular adsorbent recirculation system
SBP	Spontaneous bacterial peritonitis
SMT	Standard medical therapy
SOFA	Sequential organ failure assessment score

SPAD	Single pass albumin dialysis
SVRI	Systemic vascular resistance index
TNF	Tumor necrosis factor

### Key Points

- Supporting detoxification and synthetic functions of the failing liver is the rationale for the use of extracorporeal liver support (ECLS) systems.
- Bioartificial ECLS systems incorporate a bioreactor containing various forms of hepatocytes to provide synthetic functions.
- Artificial and bioartificial liver support devices have shown certain detoxification capabilities and biochemical improvement in patients with acute and acute-on-chronic liver failure, but their effects have failed to correlate with survival benefit.
- High Volume Plasmapheresis (HVP) is the only therapy that has demonstrated a statistically significant benefit in transplant-free survival in ALF patients.
- Further refinement of target populations and adequate endpoints, optimization of therapy delivery, and avoidance of futile therapy appear to be essential steps for future ECLS devices to become integrated in standard medical therapy for specific subpopulations of ALF and ACLF patients.

## 21.1 Introduction: The Two Syndromes of Liver Failure

### 21.1.1 Acute Liver Failure (ALF)

Acute liver failure (ALF) is defined by hepatic encephalopathy (HE) and coagulopathy within 26 weeks of the first symptoms of liver disease [1] occurring in patients without underlying chronic liver disease. The most common cause of ALF in North America and Europe is acetaminophen (APAP) [2, 3]. Particularly in APAP-induced ALF, cerebral edema and intracranial hypertension (ICH) continue to be major causes of morbidity and mortality along with multiorgan failure due to the systemic inflammatory response syndrome (SIRS) [4, 5]. Current management strategies for ALF (particularly hyperacute ALF) are directed at reducing ICH, these include osmotic agents (mannitol or hypertonic saline) [6], control of blood pressure, ammonia-lowering therapies (e.g., hemofiltration [7]) and therapeutic hypothermia (TH) [8].

### 21.1.2 Acute on Chronic Liver Failure (ACLF)

In contrast to acute liver failure, acute on chronic liver failure (ACLF) is defined as patients with cirrhosis hospitalized for an acute decompensation (AD) with associated organ failure(s) and a significantly increased risk of short term mortality [9].

ACLF usually presents as an acute deterioration in liver function over a 2–4 week period in a patient with pre-existing chronic liver disease. Similar to ALF, the lack of the metabolic and regulatory functions of the liver results in life-threatening complications that may include variceal bleeding, acute kidney injury (AKI), hepatic encephalopathy (HE), cardiovascular failure and susceptibility to infections culminating in multi-organ failure [10]. Recently the CLIF-SOFA score has demonstrated that accumulating organ failures in ACLF patients in the absence of transplant is associated with increased mortality [9].

## 21.2 Rationale for Use of ECLS in ALF and ACLF

In both ALF and ACLF, toxins accumulate as a result of impaired hepatic function and clearance. Ammonia, inflammatory cytokines, aromatic amino acids and endogenous benzodiazepines have been implicated in the development of HE and cerebral edema (ALF). Other systemic factors such as nitric oxide and cytokines have been linked with circulatory and renal dysfunction in liver failure. Pro-inflammatory cytokines and damage associated molecular patterns (DAMPs) have broad effects ranging from increased capillary permeability to modulating cell-death and immune dysregulation.

Currently, liver transplantation (LT) is the only definitive treatment for ALF and ACLF patients when poor prognostic criteria are met. Unfortunately many patients die before a suitable graft becomes available; and for those who progress to multi-organ failure, LT is not an option. For patients with APAP-ALF, the liver often maintains some regenerative capacity allowing supportive therapies and extracorporeal systems to be utilized to create or prolong a window of opportunity for LT. Ideally, these interventions would promote native liver recovery in APAP-ALF without cerebral edema/multi-organ failure, and in cases of ACLF, to establish a period of stability until an organ becomes available [11].

From a theoretic perspective, an effective extracorporeal liver support system (ECLS) should assist three major hepatic functions: detoxification, biosynthesis, and regulation.

In both ALF and ACLF, aims of ECLS would be to remove putative toxins preventing further aggravation of liver failure, to stimulate liver regeneration, and to improve the pathophysiologic features of liver failure [12]. None of the devices currently available, however, fulfil these requirements completely.

## 21.3 Extracorporeal Liver Support Systems: Artificial and Bioartificial

ECLS systems that have been tested clinically belong to one of the following two categories:

**Table 21.1** Artificial extracorporeal liver support in ALF/ACLF

Study	N	Device	Biochemical	CVS	CNS	Survival
<i>ACLF</i>						
Mitzner [18]	13	MARS	Yes	Yes	No	Yes (37.5% vs. 0% at 7 days)
Heemann [19]	24	MARS	Yes	Yes	Yes	Yes (90% vs. 55% at 30 days)
Sen [43]	18	MARS	Yes	No	Yes	No (45% in both)
Laleman [27]	18	MARS/Prometheus	Yes	No	N/A	N/A
Hassinien [20]	70	MARS	Yes	N/A	Yes	N/A
Kribben [28]	143	Prometheus	Yes	N/A		No effect on 28/90 day survival
Banares [21]	189	MARS	Yes	N/A	Yes	No effect on 28 day survival
<i>ALF</i>						
Schmidt [22]	13	MARS	Yes	Yes	N/A	No
El Banayosi [23]	27	MARS	No	N/A	N/A	Yes (50% vs. 32%) <sup>a</sup>
Saliba [24]	102	MARS	Yes	N/A	N/A	No effect on survival
Larsen [33]	182	HVP	Yes	Yes	Yes	Yes

**Biochemical improvements:** Statistically significant reduction in bilirubin, bile acids, creatinine, ammonia

N/A not assessed

<sup>a</sup>Patients may have had acute liver injury (ischemic hepatitis) and not acute liver failure

**Artificial ECLS systems:** These are based on the principles of adsorption and filtration and are aimed at removing circulating toxins by using membranes with different pore sizes and adsorbent columns.

**Bioartificial ECLS (B-ECLS) systems** are hybrid devices that incorporate hepatocytes in a bioactive platform to improve the detoxification capacity and to support synthetic hepatic function [13]. Cells origins include human (including hepatoblastoma) and porcine (Table 21.1).

## 21.4 Artificial ECLS: Detoxification and the “Albumin Hypothesis”

Albumin administration has been shown to be beneficial in spontaneous bacterial peritonitis and hepatorenal syndrome partly due to its ability to bind toxins [14]. Artificial ECLS technologies utilize albumin as a binding and scavenging molecule. Different albumin-based ECLS devices vary based on the following characteristics:

- membrane types/porosity/selectivity
- types of columns/filters
- modality of renal replacement therapy utilized
- need to have an albumin enriched dialysate
- extracorporeal volume needed

Dialysis-related techniques include **MARS** (Molecular Adsorbent Recirculation System) and **SPAD** (Single Pass Albumin Dialysis) [15]. These techniques involve dialyzing blood against an albumin-containing solution across a highly selective/small porosity (<50 kilodaltons—kDa) high-flux membrane. The blood-bound toxins are cleared by diffusion and taken up by the binding sites of the albumin dialysate. In contrast, plasma adsorption techniques such as Prometheus

(Fractionated Plasma Separation and Adsorption) and High Volume Plasmapheresis (HVP) employ more non-selective membranes (~250 kDa) and do not employ a parallel dialysate circuit.

## 21.5 Molecular Adsorbents Recirculation System (MARS)

MARS was originally developed by Stange and Mitzner [16] (Teraklin AG, Germany) in 1993. The system consists of a blood circuit, an albumin circuit and a classic “renal” circuit. Blood is dialysed across an albumin impregnated high-flux dialysis membrane; 600 mL of 20% human albumin in the albumin circuit acts as the dialysate. The albumin dialysate is subsequently cleansed via passage across two sequential adsorbent columns containing activated charcoal and anion exchange resin. These columns remove most of the albumin bound toxins. Substances with a molecular weight of more than 50 kDa, such as essential hormones and growth factors bound to albumin, are not removed because of the small pore size of the membrane [17].

## 21.6 MARS and ACLF: Clinical Studies

In 2000, Mitzner et al. reported 13 patients with ACLF and Type 1 HRS treated with MARS [18]. Patients received a mean of five treatments and did not receive vasopressors nor were any transplanted. He showed a 37.5% absolute survival benefit at day 7 vs. 0% in controls). A significant decrease in creatinine and bilirubin was also noted in the MARS group.

Subsequently, Heemann and colleagues randomized 23 patients with ACLF (19 were alcoholics) to MARS or standard medical therapy (SMT; including dialysis if necessary) [19].



**Table 21.2** Evidence for bioartificial ECLS in ALF/ACLF

Study	N	Device	Cell type	Survival
<i>ACLF</i>				
VTI-208 2015	203	ELAD	Human (Cultured C3A)	No (90 day 59 vs. 62%, $p = 0.74$ )
<i>ALF</i>				
Ellis [38]	24	ELAD	Human (Cultured C3A)	No difference in survival
Demetriou [39]	171	HepatAssist	Porcine (Cryopreserved)	No (30 day 71% vs. 62%, $p = 0.26$ )

**Biochemical improvements:** Statistically significant reduction in bilirubin, bile acids, creatinine and ammonia

Inclusion criteria included bilirubin  $> 340 \mu\text{mol/L}$ , HE  $>$  Grade 2 and AKI. At day 30, 11/12 patients in the MARS group were still alive, compared to only 6/11 in the control group ( $p < 0.05$ ). There were also statistically significant decreases in bilirubin (43%) and bile acids (29%) in the MARS group but not in the control group. A statistically significant increase in mean arterial pressure (MAP) ( $p < 0.05$ ) as well as reductions in creatinine and HE grade ( $p < 0.06$ ) were noted in the MARS group.

In 2007, Hassanein and colleagues published a randomized controlled study of 70 ACLF patients with grade 3 or 4 HE who received either MARS ( $n = 39$ ) or SMT ( $n = 31$ ) [20]. The need for ventilation and the use of sedation were equal in both groups. Patients in the MARS group received therapy for 6 h daily for 5 days or until a 2-grade improvement in HE was achieved. In the MARS group, 34% achieved a 2-grade improvement in HE vs 19% in the SMT group ( $p = 0.044$ ). This study was not powered to assess mortality.

The results of the largest randomized trial of the use of MARS in ACLF (**RELIEF** study) were reported by Banares and colleagues in 2013 [21]. In this study, 189 patients with ACLF from 19 European centers were randomly assigned to receive either MARS plus SMT ( $n = 95$ ) or SMT alone ( $n = 94$ ). The primary endpoint of the study was 28-day survival. Patients randomly assigned to the MARS arm received up to ten 6- to 8-h sessions of MARS. Improvement of HE was also more frequent in the MARS arm (from grade II–IV to grade 0–I; 63% vs. 38%;  $p = 0.07$ ). However there was no difference in 28-day survival between the MARS and SMT groups either by intention-to-treat or per-protocol analysis (60.7% vs 58.9%; 60% vs 59.2% respectively). Adverse events were similar in both groups, a fact that has been observed across the different studies.

## 21.7 MARS and ALF

In 2003, Schmidt and colleagues conducted a study to assess the effects of a single 6-h MARS treatment on hemodynamics, oxygen consumption and biochemical profile in 13 ALF patients (APAP  $n = 10$ ) with HE grade III/IV [22]. Eight received MARS therapy and 5 received SMT with cooling to match hypothermia induced by MARS. Systemic vascular resistance index (SVRI) increased by 46% in the MARS

group during the 6-h run treatment versus a 6% increase in the controls ( $p < 0.0001$ ). MAP also increased in the MARS group ( $p < 0.001$ ), while pressure was unchanged in controls. Compared to baseline, there were significant reductions in bilirubin, creatinine, and urea ( $p < 0.05$ ) but not in ammonia in the MARS group. Survival was similar between groups. In a controlled study of 27 patients treated for ALF due to cardiogenic shock [23], El Banayosy demonstrated non-significant reductions in conjugated and total bilirubin and mortality (Table 21.2). However, it is unclear whether this population truly met criteria for ALF, as there is no mention of grade of HE.

The most robust study of MARS in ALF was a recently published randomized, controlled trial performed in 16 French transplant centers (FULMAR study) by Saliba and colleagues [24]. This study compared the impact of MARS plus SMT versus SMT alone in patients with ALF fulfilling transplant criteria. Fifty-three patients were randomized to receive MARS therapy whereas 49 had SMT. Overall there were no significant differences in 6-month survival between the MARS (85%) vs SMT (76%) groups ( $p = 0.28$ ). However, a major confounder was that the median listing-to-transplant time was only 16.2 h, and 75% of enrolled patients underwent transplant within 24 h. In the MARS group, 14/53 patients did not complete at least 5 h of MARS therapy prior to LT or death. Hence while overall negative, this study may have been underpowered to show a potential benefit in 6-month transplant-free survival in APAP-ALF patients (MARS 85% vs. SMT 68%,  $p = 0.40$ ), a group with greater potential for hepatic recovery.

## 21.8 MARS and Inflammatory Profile

Stadlbauer et al. assessed cytokine levels in eight patients with ACLF of diverse etiologies undergoing alternating treatments with MARS and Prometheus in a random cross-over design [25]. Thirty-four treatments (17 MARS, 17 Prometheus) were available for analysis. While measurable plasma clearances were detected for IL-6, IL-8, IL-10 and TNF- $\alpha$ , none were significant for MARS or Prometheus. Based on these studies, MARS does not appear to have a significant impact on the inflammatory profile in ACLF.

## 21.9 SPAD: Single Pass Albumin Dialysis

Single Pass Albumin Dialysis or SPAD differs from MARS in that it utilizes a standard continuous renal replacement therapy system without any additional columns or circuits. Blood is dialysed against a standard dialysis solution with the addition of 4.4% albumin in the dialysate. SPAD has been evaluated in a case-controlled fashion in APAP-ALF but failed to show biochemical or mortality improvements [26].

## 21.10 Prometheus: Fractionated Plasma Separation and Adsorption

Prometheus (Fresenius, Hamburg) or fractionated plasma separation and adsorption (FPSA) was initially introduced in 1999. In this circuit, patient plasma is fractionated through an albumin-permeable filter with a cut-off of 250 kDa. Albumin and other plasma proteins cross the membrane and pass across two columns in series; one an anion-exchange column, another a neutral resin adsorber. The cleansed albumin/plasma is returned to the standard blood pool circuit where it is then treated by conventional high-flux haemodialysis.

To date there have been few significant controlled studies examining the impact of Prometheus, both examined ACLF patients only. Laleman and colleagues compared the hemodynamic effects of Prometheus with MARS in 18 patients with ACLF secondary to severe alcoholic hepatitis (Maddrey score > 60) [27]. Six patients received MARS, six received Prometheus and six received SMT (including renal replacement therapy). After 3 consecutive days of therapy (mean ~ 6 h), both MARS and Prometheus reduced serum bilirubin ( $p < 0.005$ ), MARS increased MAP ( $\Delta +9$  mm Hg,  $p < 0.05$ ) and SVRI ( $\Delta +220$  dyne.s/cm<sup>5</sup>/m<sup>2</sup>,  $p < 0.05$ ) compared with Prometheus. No difference in hemodynamics was noted between Prometheus and SMT. Levels of endogenous norepinephrine, aldosterone and vasopressin were reduced ( $p < 0.05$ ) in the MARS group while there was no statistically significant change in the Prometheus or SMT arms.

In 2012, Kribben and colleagues reported the HELIOS trial; a prospective study of 145 ACLF patients who were randomly assigned to receive Prometheus plus SMT versus SMT alone [28]. Primary endpoints of the study were the probability of survival at days 28 and 90, irrespective of LT. Both groups were similar at the baseline. Serum bilirubin level decreased significantly in patients randomly assigned to receive FPSA compared with the group receiving SMT alone. In an intention-to-treat analysis, the 28-day survival was similar between Prometheus (66%) and the SMT (63%) groups ( $p = 0.70$ ) as was 90-day survival (Prometheus 47% vs. SMT 38%,  $p = 0.35$ ). Baseline factors independently

associated with poor prognosis were a high Sequential Organ Failure Assessment (SOFA) score, gastrointestinal bleeding, spontaneous bacterial peritonitis, AKI, and the combination of alcoholic and viral etiologies of liver disease. Similar to RELIEF (MARS), HELIOS may have suffered from confounding by indication; ACLF patients who were candidates for LT have a potential different natural history than ACLF patients who were not LT candidates.

## 21.11 High Volume Plasmapheresis

High volume Plasmapheresis (HVP) with fresh frozen plasma is an established therapy used for immunologically-driven disorders. Case series of HVP in patients with ALF have been shown to be safe [29, 30], to decrease the severity of hepatic encephalopathy, decrease vasopressor requirements [31, 32]. Recently, Larsen and colleagues published the first artificial ECLS study in ALF patients to demonstrate a statistically significant benefit in transplant-free survival using HVP [33]. They prospectively randomized 183 ALF patients (1998–2010) in three European centres, of which 91 patients received SMT and 92 received HVP above and beyond SMT. HVP was defined as 15% of ideal body weight (8–12 L of fresh frozen plasma) with individual runs lasting approximately 9 h per treatment. Patients received a mean of 2.4 therapies with only one patient in the HVP arm not receiving the therapy due to early LT. In an intention-to-treat analysis, survival to hospital discharge was 58.7% for patients treated with HVP versus 47.8% for the patients who received SMT alone (Hazard Ratio for HVP vs. SMT with stratification for LT 0.56; [95% CI 0.36 to 0.86;  $p = 0.0083$ ]). Biochemical markers (INR, bilirubin, ammonia) improved significantly in the HVP group compared with controls. Furthermore, in a nested cohort study of a subset of 30 ALF patients, patients undergoing HVP had significantly reduced circulating levels of damage-associated molecular patterns (DAMPs; including circulating histone-associated DNA), TNF- $\alpha$ , and IL-6. Furthermore, phenotypic markers of monocyte activation neutrophil activation (IL-8 expression) were down-modulated; suggesting that HVP suppresses the systemic inflammatory response associated with ALF.

## 21.12 Artificial ECLS: Adverse Effect Profile

Hemostasis is the result of a complex interaction between procoagulant, anticoagulant and fibrinolytic proteins, many of which may be affected by liver failure and furthermore by ECLS [34]. Theoretically, less selective systems such as Prometheus could potentially be at a higher risk than MARS due to the larger pore size of filters employed. Some artificial ECLS circuits require heparin [35] or citrate for anticoagulation

which may further exacerbate coagulation abnormalities [36]. Faybik and colleagues described 33 patients undergoing 61 MARS treatments [37] (15 with ALF, 15 with ACLF, three with allograft dysfunction post-transplant). Although there was a statistically significant decrease in platelets and fibrinogen, platelet function as measured by thromboelastography was unaffected. Nonetheless, larger randomized controlled studies of MARS, Prometheus and HVP in ALF and ACLF have not shown a significant increase in adverse events including bleeding over SMT [21, 24, 28, 33].

### 21.13 Bioartificial ECLS: Design

In theory, bioartificial ECLS platforms could have advantages over artificial ECLS by providing synthetic replacement as well as detoxification functionality, particularly in APAP-ALF where this is significant potential for hepatic recovery. They require a cell source which have been traditionally been derived from human or porcine hepatocytes. What has limited their widespread evaluation and adoption has been their complex nature; necessity for a critical bioactive mass, more complex cumbersome technology, cost and in cases where porcine hepatocytes cell lines have been employed, the risk of xenotransmission. To date, the vast majority of studies that have assessed the applicability and efficacy of bioartificial ECLS in ALF and ACLF have included small numbers of patients and been uncontrolled. To date two devices have been evaluated in detail; Extracorporeal Liver Assist Device (ELAD) and HepatAssist.

### 21.14 Bioartificial ECLS in ALF

ELAD is based on a platform of human-derived hepatoblastoma cells. It has been evaluated in ALF by Ellis and colleagues in 24 patients, of whom seven met poor prognostic criteria. Patients were evenly randomized to ELAD plus SMT vs. SMT [38]. Patients were stratified by the absence (group I,  $n = 17$  patients) or presence (group II,  $n = 7$  patients) of meeting poor prognostic criteria. However, there were no differences in survival in the low risk (78% vs 75% in group I) or high risk (33% vs 25% in group II) groups [38]. More recently, a randomized controlled trial of ELAD therapy in the treatment of severe alcoholic hepatitis has been concluded, and the results have been published in abstract form [39]. In this study (VTI-208), 203 patients with severe alcoholic hepatitis (defined as a Maddrey's discriminant function  $> 32$ ) and a MELD  $\leq 35$  were randomized to 3–5 days of ELAD therapy ( $n = 96$ ) or SMT ( $n = 107$ ). The primary endpoint of the study was overall survival up to 91 days. In an intention-to-treat (ITT) analysis, there was no significant difference in survival (52.1% vs. 52.3%, HR 1.027,  $p = 0.9$ ).

However, in a pre-defined subgroup of patients with a MELD  $< 28$  ( $n = 120$ ), ELAD was associated with a trend towards higher overall survival to 91 days (71% vs. 57%,  $p = 0.077$ ). Based on this subgroup analysis that is hypothesis generating, a subsequent study is planned that is designed to assess the efficacy of ELAD in a less sick population of alcoholic hepatitis patients. HepatAssist incorporates porcine-purified hepatocytes in a bioreactor and has been evaluated in a large-scale, randomized, multicenter clinical trial [40]. Dimitriou and colleagues randomly assigned 171 patients with ALF or with primary nonfunction after LT that were randomly assigned to receive SMT or SMT plus support with the HepatAssist system. The primary endpoint of the study was 30-day survival (with or without LT) and adjusted by confounding factors in a multivariate model. The number of HepatAssist treatments ranged from 1 to 9 (mean, 2.9) per patient. Overall, 30-day survival was similar in groups in the entire cohort (HepatAssist 71% vs. SMT 62%,  $p = 0.26$ ) as well as after excluding primary non-function patients ( $p = 0.12$ ). The trial was prematurely stopped because of futility in the predetermined safety interim analysis. **Is it wise to pool ECLS data in meta-analysis for ALF or ACLF patients?**

Due to the volume of underpowered studies, theoretically metaanalysis/metaregression could aid in determining if ECLS has added merit not defined in individual studies. However several systematic reviews and meta-analyses have been published in recent years with heterogeneous results. Kjaergard and colleagues pooled data for ECLS (both artificial and bioartificial) separately for ALF and ACLF from 12 randomized trials [41]. Compared with SMT, ECLS had a significant beneficial effect on HE (risk ratio [RR], 0.67; 95% CI, 0.52–0.86), but they had no significant effects on mortality (RR, 0.86; 95% CI, 0.65–1.12). Meta-regression analysis indicated that the effect of liver support systems depended on the type of liver failure; ECLS appeared to reduce mortality by 33% in ACLF (RR, 0.67; 95% CI, 0.51–0.90) but not in ALF (RR, 0.95; 95% CI, 0.71–1.29). In contrast, the meta-analysis by Stutchfield and colleagues concluded that ECLS (both artificial and bioartificial) significantly improved survival in ALF (RR, 0.70;  $p = 0.05$ ) but not in ACLF (RR, 0.87;  $p = 5.37$ ) [42]. Finally, the most recent meta-analysis, which included studies from 1973 to 2012, found a decrease in mortality in patients with ACLF patients treated with artificial ECLS (RR, 0.80; 95% CI, 0.66–0.96,  $p = 5.018$ ) and in patients with ALF treated with bioartificial ECLS (RR, 0.69; 95% CI, 0.50–0.94;  $p = 0.018$ ) [43]. These conflicting results from these meta-analyses suggest significant confounding/bias from observational studies included. Given the heterogeneity in these trials in follow-up period, etiology of ALF/ACLF and severity of illness/organ failure, divergent results/conclusions are hardly surprising. Given that none of these studies included recent large MARS

(RELIEF, FULMAR) or HVP studies, none of these studies likely answer questions raised from individual trials.

## 21.15 Discussion: Future directions

There continues to be great interest and potential for ECLS. At present it is difficult to make an evidence-based recommendation supporting artificial ECLS. Of this group, MARS is the best-studied albumin dialysis technology in ALF and ACLF. While studies have consistently demonstrated biochemical improvement and improvement in hepatic encephalopathy with MARS [20], recent large randomized studies in ACLF (RELIEF) [21] and ALF (FULMAR) [24] showed no survival benefit. The HELIOS study examining Prometheus in ACLF was also disappointing [28]. These studies shared some common methodological limitations in study design. Within studies in ALF and ACLF, heterogeneous groups of patients with varying etiologies with different natural histories were often lumped together. Several studies did not stratify patients based on severity of illness (e.g. ACLF ~ MELD, CLIF-SOFA) and hence it is difficult to assess patient matching and furthermore the impact of underlying disease on patient mortality with or without treatment. Furthermore due to co-interventions such as LT, not all patients received pre-specified durations of ECLS therapy. When examining the RELIEF and HELIOS trials, it may have been more parsimonious to examine only ACLF patients who were candidates for LT as ACLF patients with multiorgan failure portends poor outcomes [9]. Successfully bridging patients to LT may warrant further consideration as the primary endpoint over 30–90 day survival.

In ALF, it may be wise to focus future studies on acetaminophen-induced ALF patients as they have the highest chance of spontaneous recovery of hepatic function and ECLS could potentially have a role even in patients who are not candidates for LT due to psychosocial or medical contraindications as a bridge to recovery. The FULMAR study was underpowered to evaluate this subgroup, though this was the only subgroup with a potential mortality difference [24]. One explanation for this is that the predominant mechanism responsible for the development of cerebral edema/multiorgan failure in hyperacute ALF is activation of and release of pro-inflammatory cytokines DAMPs as a result of massive hepatocyte necrosis [43]. In the only artificial ECLS study to show a benefit in transplant free survival, Larsen and colleagues demonstrated in ALF patients undergoing HVP that patients in the HVP group had significantly reduced circulating levels of DAMPs and proinflammatory cytokines with concomitant decrease in neutrophil activation [33]. Dampening of the SIRS cascade was also consistent with the observed improvement in

evidence of multiorgan failure as measured by SOFA and CLIF-SOFA. Given that APAP-ALF patients present early with multiorgan failure and upregulated SIRS response, studies of future artificial and bioartificial ECLS devices should consider their impact on the proinflammatory cascade, especially in APAP-ALF.

While it is clear that current artificial and bioartificial ECLS devices have limitations, potentially the greatest area for future research is in the improvement/refinement of bioartificial platforms. To date studies of ELAD (human derived hepatocytes) and HepatAssist (porcine hepatocytes) have been disappointing [38, 40]. Further research into other functional cell sources (genetically modified liver cell lines, humanized pig cells, hepatocyte spheroids) is ongoing [44]. Future studies will likely have to weigh the added levels of complexity and expense compared with purely detoxifying systems such as HVP.

Irrespective of advances in technologies, future studies will need to avoid the methodological pitfalls of the past. Target patient populations should be homogenous with respect to etiologies (e.g. APAP-ALF) or natural history (e.g. only ACLF patients listed for LT). Patients enrolled into future trials should be comparable with respect to severity of illness (e.g. number of organ failures, CLIF-SOFA) are target subpopulations need to be delineated further to avoid futile therapy. Other concomitant therapies (mechanical ventilation, antibiotics, and renal replacement therapy) will need to be consistent so that outcomes are not impacted by co-interventions.

**Acknowledgements** None.

## References

1. O'Grady JG, Williams R. Classification of acute liver failure. *Lancet*. 1993;342:743.
2. Fagan E, Wannan G. Reducing paracetamol overdoses. *BMJ*. 1996;313:1417–8.
3. Larson AM, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005;42:1364–72.
4. Ware AJ, D'Agostino AN, Combes B. Cerebral edema: a major complication of massive hepatic necrosis. *Gastroenterology*. 1971;61:877–84.
5. Bernal W, Wendon J. Acute liver failure; clinical features and management. *Eur J Gastroenterol Hepatol*. 1999;11:977–84.
6. Murphy N, et al. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology*. 2004;39:464–70.
7. Slack AJ, et al. Ammonia clearance with haemofiltration in adults with liver disease. *Liver Int*. 2014;34:42–8.
8. Jalan R, et al. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology*. 2004;127:1338–46.
9. Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426–37. 37.e1–9



10. Sen S, Williams R, Jalan R. The pathophysiological basis of acute-on-chronic liver failure. *Liver*. 2002;22(Suppl 2):5–13.
11. Sen S, Williams R, Jalan R. Emerging indications for albumin dialysis. *Am J Gastroenterol*. 2005;100:468–75.
12. Nyberg SL. Bridging the gap: advances in artificial liver support. *Liver Transpl*. 2012;18(Suppl 2):S10–4.
13. Allen JW, Hassanein T, Bhatia SN. Advances in bioartificial liver devices. *Hepatology*. 2001;34:447–55.
14. Evans TW. Review article: albumin as a drug—biological effects of albumin unrelated to oncotic pressure. *Aliment Pharmacol Ther*. 2002;16(Suppl 5):6–11.
15. Mitzner S, et al. Albumin regeneration in liver support—comparison of different methods. *Ther Apher Dial*. 2006;10:108–17.
16. Stange J, et al. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. *Artif Organs*. 1993;17:809–13.
17. Stange J, et al. Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. *Artif Organs*. 1999;23:319–30.
18. Mitzner SR, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. *Liver Transpl*. 2000;6:277–86.
19. Heemann U, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. *Hepatology*. 2002;36:949–58.
20. Hassanein TI, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. *Hepatology*. 2007;46:1853–62.
21. Banares R, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. *Hepatology*. 2013;57:1153–62.
22. Schmidt LE, et al. Systemic hemodynamic effects of treatment with the molecular adsorbents recirculating system in patients with hyperacute liver failure: a prospective controlled trial. *Liver Transpl*. 2003;9:290–7.
23. El Banayosy A, et al. First use of the Molecular Adsorbent Recirculating System technique on patients with hypoxic liver failure after cardiogenic shock. *Asaio J*. 2004;50:332–7.
24. Saliba F, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. *Ann Intern Med*. 2013;159:522–31.
25. Stadlbauer V. Effect of extracorporeal liver support by MARS and Prometheus on serum cytokines in acute-on-chronic liver failure (AoCLF). *Crit Care*. 2006;10:1–20.
26. Karvellas CJ, et al. A case-control study of single-pass albumin dialysis for acetaminophen-induced acute liver failure. *Blood Purif*. 2009;28:151–8.
27. Laleman W, et al. Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. *Crit Care*. 2006;10:R108.
28. Kribben A, et al. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology*. 2012;142:782–9. e3.
29. Kondrup J, et al. High volume plasma exchange in fulminant hepatic failure. *Int J Artif Org*. 1992;15:669–76.
30. Nakamura T, et al. Effect of plasma exchange on serum tissue inhibitor of metalloproteinase 1 and cytokine concentrations in patients with fulminant hepatitis. *Blood Purif*. 2000;18:50–4.
31. Larsen FS, et al. Systemic vascular resistance during high-volume plasmapheresis in patients with fulminant hepatic failure: relationship with oxygen consumption. *Eur J Gastroenterol Hepatol*. 1995;7:887–92.
32. Larsen FS, et al. Cerebral blood flow, oxygen metabolism and transcranial Doppler sonography during high-volume plasmapheresis in fulminant hepatic failure. *Eur J Gastroenterol Hepatol*. 1996;8:261–5.
33. Larsen FS, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol*. 2015. <https://doi.org/10.1016/j.jhep.2015.08.018>.
34. Doria C, et al. Thromboelastography used to assess coagulation during treatment with molecular adsorbent recirculating system. *Clin Transplant*. 2004;18:365–71.
35. Tan HK, et al. Anticoagulation minimization is safe and effective in albumin liver dialysis using the molecular adsorbent recirculating system. *Artif Organs*. 2007;31:193–9.
36. Meijers B, et al. A prospective randomized open-label crossover trial of regional citrate anticoagulation vs. anticoagulation free liver dialysis by the Molecular Adsorbents Recirculating System. *Crit Care*. 2012;16:R20.
37. Faybik P, et al. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. *Crit Care*. 2006;10:R24.
38. Ellis AJ, et al. Pilot-controlled trial of the extracorporeal liver assist device in acute liver failure. *Hepatology*. 1996;24:1446–51.
39. Thompson JA, et al. The effect of extracorporeal C3a cellular therapy in severe alcoholic hepatitis—the Elad trial. *Hepatology*. 2015;62(6, Suppl), Abstract # LB-1, 1379A.
40. Demetriou AA, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg*. 2004;239:660–7. discussion 7–70.
41. Kjaergard LL, et al. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. *JAMA*. 2003;289:217–22.
42. Stutchfield BM, Simpson K, Wigmore SJ. Systematic review and meta-analysis of survival following extracorporeal liver support. *Br J Surg*. 2011;98:623–31.
43. Antoniadou CG, et al. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol*. 2008;49:845–61.
44. Glorioso JM, et al. Pivotal preclinical trial of the spheroid reservoir bioartificial liver. *J Hepatol*. 2015;63:388–98.

Mihir Shah and Rahul Nanchal

### Abstract

Liver function can be assessed by two broad categories of tests – static and dynamic. Traditionally static tests such as bilirubin, transaminases, albumin and coagulation factors amongst others have been used to assess liver function. Static tests are used to determine extent of hepatocellular injury, type of jaundice, monitor function in liver disease or as part of scoring systems such as the Model for End Stage Liver Disease (MELD). Dynamic tests are perhaps appropriate for critically ill patients because of their ability to detect changes in liver function quickly. Dynamic tests assess liver function by determining hepatic ability to eliminate or metabolize defined substances over time. They can be repeated and provide a more global assessment of liver function.

### Keywords

Liver function tests • Static tests • Dynamic tests • Indocyanine green clearance • Monoethylglycincylidide • Critical illness • Hepatic function • Hepatic blood flow • Hepatic metabolism

## 22.1 Introduction

Assessing liver function in a critically ill patient is very important, as the liver is a discrete organ, which performs many different inter-relating functions.

The liver is the largest organ of the body, contributing about 2% of the total body weight, or about 3–4 lbs in an average human. The liver receives dual blood supply from the portal vein and hepatic arteries. The liver receives about 1050 ml/min of blood flow from the portal vein and around 300 ml/min of blood flow from the hepatic artery making it a total of 1350 ml/min of blood flow through the liver, comprising approximately 27% of resting cardiac output [1].

M. Shah, M.D. • R. Nanchal, M.D., M.S. (✉)  
Department of Medicine, Medical College of Wisconsin,  
Milwaukee, WI, USA  
e-mail: [mishah@mcw.edu](mailto:mishah@mcw.edu); [Rnanchal@mcw.edu](mailto:Rnanchal@mcw.edu)

## 22.2 Physiology

The basic functional unit of the liver is called liver lobule. It is constructed around the central vein that empties into the hepatic vein and subsequently into the inferior vena cava. The lobule is primarily composed of hepatic cells, which radiates from the central veins like spokes in a wheel. In addition to the hepatic cells the venous sinusoids are lined by: [1] typical endothelial cells and [2] Kupffer cells (liver macrophages).

Liver is an expandable organ and stores large quantities of blood in its blood vessels. It stores around 450 ml of blood in hepatic sinuses which comprises of almost 10% of the body's total blood volume [1]. It can store up to 1–1.5 L if the right atrial pressure is high causing significant back pressure and venous congestion.

The pores of the hepatic sinusoids are highly permeable compared to the capillaries and hence allow ready passage of

the proteins and fluids into the space of Disse. The protein concentration of the lymph draining from the liver is around 6 g/dl, which is slightly less than the plasma concentration.

The hepatic macrophage system serves as a blood cleansing system. The blood flowing through intestinal capillaries gathers many bacteria from the intestine. The blood sample taken from the portal vein almost always grows colonic bacteria whereas growth of colonic bacteria in the systemic blood is extremely rare. Kupffer cells (liver macrophages) engulf the bacteria within 0.01 s of contact. Probably less than 1% of the bacteria entering the portal blood from the intestines succeed in passing through the liver into the systemic circulation.

Metabolic Function of Liver [1] are enumerated below:

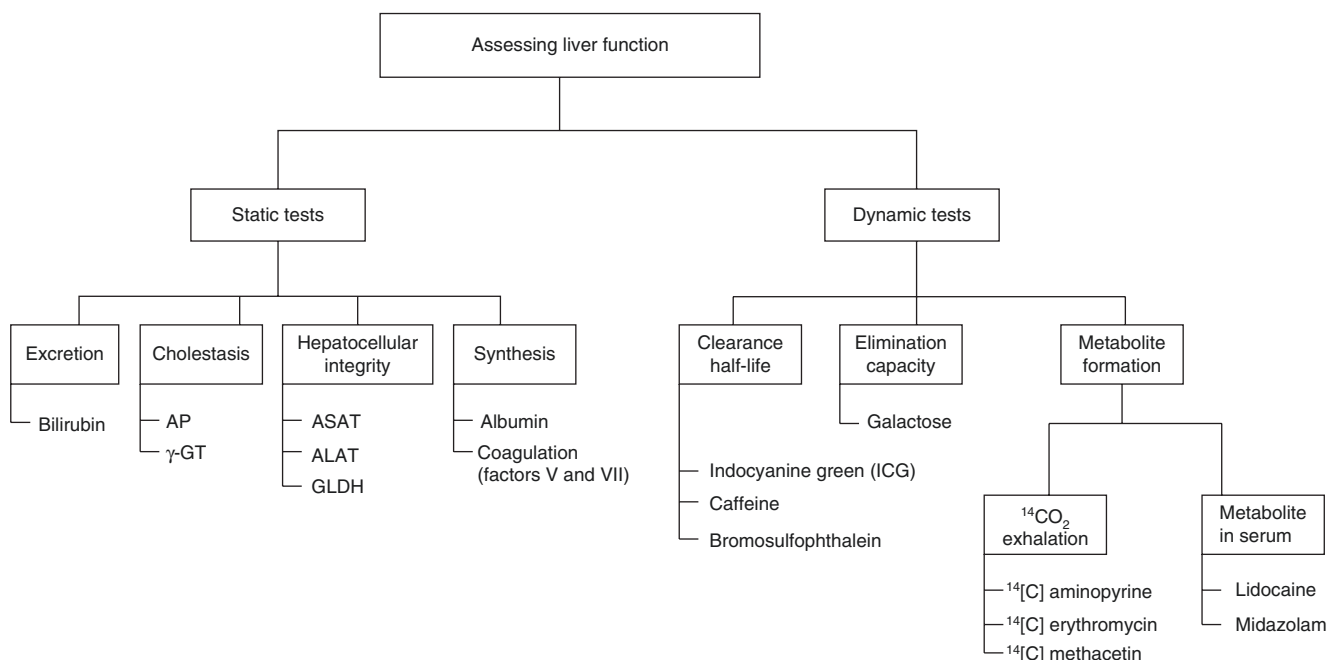
1. Carbohydrate Metabolism:
  - Storage of Large amount of Glycogen.
  - Conversion of galactose and fructose to glucose.
  - Gluconeogenesis from fat and proteins.
  - Formation of many chemical compounds from intermediate products of carbohydrate metabolism.
2. Fat Metabolism:
  - Oxidation of Fatty acids to supply energy for other body functions.
  - Synthesis of large quantities of cholesterol, phospholipids and lipoproteins.
  - Synthesis of fat from proteins and carbohydrates.
3. Protein Metabolism:
  - Deamination of amino acids.

- Formation of urea for removal of ammonia from the body.
  - Formation of plasma proteins (essentially all plasma proteins with exception of gamma globulins are formed in liver).
  - Inter-conversion of various amino acids and synthesis of other compounds from amino acids.
4. Storage site for Vitamins.
  5. Liver is a site for production of various factors used in coagulation cascade, like prothrombin, fibrinogen, accelerator globulin, factor VII and several other factors. Vitamin K is required for the formation of prothrombin, Factors VII, IX and X.

## 22.3 Static and Dynamic Tests

Traditionally liver function has been assessed in a critically ill patient by static tests, such as serum activity of liver enzymes, protein synthesis by the liver (coagulation factors, albumin) and bilirubin.

On the other hand dynamic assessment of the complex liver functions, like clearance of substances (Indocyanine Green; ICG) or formation of metabolites (lidocaine to monoethylglycinyldide {MEGX} or  $^{14}\text{C}$ -aminopyrine), has been shown to reveal otherwise hidden hepatocellular functions (Fig. 22.1) [2].



**Fig. 22.1** Assessing Liver Function – Dynamic and Static Tests

### 22.3.1 Static Tests

Static Test merely allows spot check and a very restricted description of the liver function.

Pros of Static Testing:

- Easy to perform.
- Easily available in every institute.
- Not very labor intensive.

Cons of Static Testing:

- Limited by the fact that they do not enable tracking changes in the liver function very quickly.
- These tests may be affected by non-hepatic causes.
- Less sensitive in predicting outcomes compared to dynamic testing [3].

Bilirubin:

- Physiologically, bilirubin (product of heme metabolism) undergoes uptake by hepatocellular cells and undergoes conjugation with glucuronic acid to form direct bilirubin which is water soluble and gets excreted in bile.
- Hyperbilirubinaemia can be divided into three different pathologies:  
Pre-hepatic (e.g. hemolysis).  
Intra-hepatic (e.g. Hepatitis, liver cell injury due to various toxins).  
Post-hepatic (e.g. Cholestasis).
- The quantification of direct and indirect bilirubin in combination with liver enzymes can help differentiate between the different types of pathologies.
- It is one of the most widely used markers for liver dysfunction in ICU and different scoring systems.

Liver Specific Enzymes:

- Transaminases (AST/ALT) activity in the serum has been clinically used for the assessment of liver function and liver injury.
- Enzymes may reflect the extent of hepatocellular necrosis (Transaminases) or cholestasis (alkaline phosphatase or  $\gamma$ -glutamyl transferase).
- Serum activity of the transaminases are increased in various liver diseases, however are only limited to prognostic values and do not reflect the extent of the liver cell necrosis appropriately [4].
- Alkaline Phosphate helps in hydrolysis of organic phosphate esters and though not exclusively present in the liver, is used as a marker of cholestasis.
- $\gamma$ -Glutamyl transferase enzyme is responsible for transfer of  $\gamma$ -glutamyl group between peptides. It is increased in cholestasis, chronic alcohol use and anti-convulsive treatment.

Hepatocellular synthetic function:

- It can be assessed by different parameters of the coagulation system (e.g. PT/INR, activated thromboplastin time) or albumin concentration.
- Characterizes the extent of functional liver mass loss and liver synthetic function.

### 22.3.2 Dynamic Testing

The dynamic tests assess the liver function by determining the liver's ability to eliminate or metabolize defined substances in time.

Pros of Dynamic Testing: [5, 6]

- Gives an instant idea of the function at the moment of measurement and can be repeated shortly thereafter.
- Gives a more global measure of liver function.
- Can be used to detect rapid changes in liver function associated with critical illness.

Cons of Dynamic Testing:

- Not readily available.
- Time consuming and technically cumbersome.
- Vary considerably with respect to different hepatic partial functions and its utility is questionable in those clinical scenarios.

Dynamic tests commonly used are listed and described below [5]

1. Indocyanine Green (ICG) clearance Test,
2. Caffeine Test,
3. Bromosulphophthalein (BSP) clearance,
4. Amino Acid clearance,
5. Monoethylglycine xylidide (MEGX) test and
6. Aminopyrine test.

#### 22.3.2.1 Indocyanine Green (ICG) Clearance Test

Indocyanine Green (ICG) is a water-soluble fluorescent dye, with a spectral absorption at 800 nm in blood plasma [7]. When it administered intravenously, it binds to plasma proteins like albumin and lipoproteins and is selectively taken up by hepatocytes. It is eliminated into the bile unchanged and does not undergo enterohepatic recirculation.

Removal of ICG depends on [7, 8]:

- Hepatic Blood flow,
- Function of hepatocytes,



– Biliary excretion.

ICG is a safe substance, as side effects are very rare (1:40,000). Over dosage has not been described [9]. ICG should be used with caution in patients with iodide allergy or thyrotoxicosis as it is an iodine-based dye [10].

Due to the above features, ICG elimination is considered to correlate with hepatic function and thereby useful as dynamic liver function test. ICG elimination may be expressed as half-life time, blood clearance or plasma disappearance rate (ICG-PDR). For ICG-PDR, initial concentration at time 0 is considered 100% and ICG-PDR is percentage change over time (percent per minute). Today, ICG-PDR can be measured at bedside with a non-invasive transcutaneous system and the result can be obtained in 6–8 min [11]. Normal values for ICG-PDR is over 18%/min. ICG-PDR can be assessed: using various techniques. The gold standard is serial blood sampling after injection of ICG and spectrophotometric analysis to obtain the concentration. A non-invasive technique has also been developed, using transcutaneous pulse spectrophotometry. This measures the arterial concentration based on the difference in absorbance between oxy-hemoglobin and ICG.

Limitations of ICG-PDR test:

1. Factors that compromise hepatic hemodynamics, i.e. thrombosis or intrahepatic shunting, will result in changes in the hepatic blood flow and thereby change the clearance rate of ICG. The result is 'global' view of liver function and does not explain local changes.
2. In steatosis and hepatitis, some of the transport polypeptides can be downregulated, thus affecting the uptake of ICG, making all the measurements lower [12].
3. Hyperbilirubinemia ( $>51 \mu\text{mol/l}$ ) can reduce the ICG-PDR probably because ICG and bilirubin use the same transport carrier and competitively inhibit each other's uptake.
4. It measures global liver function and does not measure local variations.

Utility in ICU Setting

Traditionally ICG-PDR has been used to assess liver function in patients undergoing hepatectomy or liver transplantation as a supplement to other tests.

Kortgen et al. prospectively investigated the development of liver dysfunction in patients with severe sepsis who were admitted to ICU. They calculated APACHE II score, MOD (Multiple Organ Dysfunction) Score and SOFA (Sepsis-related Organ Failure Assessment) score daily. ICG-PDR was measured via a catheter in the femoral artery and they followed routine laboratory tests for liver function. Non-survivors had higher APACHE II, MOD and SOFA scores at inclusion. ICG-PDR was significantly higher in survivors

at day 1 and 3, whereas conventional markers for liver damage did not predict any difference in the two groups. ICG-PDR less than 8%/min predicted death with sensitivity of 81% and specificity of 70%. They conclude that ICG-PDR is superior to conventional liver markers in prognosis [13].

Similarly, Sakka et al. also analyzed the prognostic value of ICG-PDR in critically ill patients. They used the lowest value of ICG-PDR and found that ICG-PDR was significantly lower in non-survivors independent of diagnosis in patients with sepsis. The mortality was 80% in patients with ICG-PDR  $<8\%/min$  and survival was 80% in patients with ICG-PDR  $>16\%/min$ .

#### 22.3.2.2 Caffeine Test

Caffeine is physiologically metabolized in the liver to paraxanthine, theobromine and theophylline. The metabolite/caffeine ratio calculated from blood samples after 4, 8 and 12 h after 300 mg of oral caffeine has been suggested for evaluation of hepatic dysfunction.

Elimination of caffeine takes significantly longer and hence the metabolite to caffeine ratios are lower in cirrhotic patients compared to healthy volunteers.

In critically ill patients there is limited data available for the validity of the test and this test requires complex laboratory equipment (high performance liquid chromatography, HPLC). Thus caffeine test is limited and is not commonly used in critically ill patients.

#### 22.3.2.3 Bromosulphophthalein Clearance

BSP when injected intravenously is extracted rapidly and exclusively by the liver. %mg/kg of BSP is administered and serum determinations are made at 30 and 45 min. In healthy individuals, less than 10% is left in 30 min and less than 5% is left in 45 min.

This test which may be associated with severe systemic reactions (possibly fatal) and requires special laboratory equipment has been largely abandoned from clinical use [14].

#### 22.3.2.4 Monoethylglycinoxylidide (MEGX) Test

The MEGX test is based on hepatic conversion of lidocaine to MEGX which is related to cytochrome P450 (CYP450) system. MEGX test like all the other dynamic tests, depends on hepatic blood flow and hepatic metabolic capacity.

In practice, blood samples for determination of MEGX prior to and 15 min after intravenous injection of lidocaine (1 mg/kg) have been suggested [15]. Quantification of MEGX serum concentration requires immunoassay, HPLC or gas chromatography.

In critically ill patients, Schroter et al. showed that MEGX concentration at fourth day in ICU amongst survivors was 53 ng/ml, significantly higher than non-survivors (23 ng/ml) [16]. In another study, MEGX concentration on third ICU

day had highest prognostic value compared to all liver function test including ICG-PDR [17].

In contrast to ICG-PDR, the MEGX test does not allow the bedside evaluation of liver function. MEGX test is related to metabolism of lidocaine by CYP450 system and various drug interactions makes the interpretation of this test in critically ill patients challenging. For instance, antibiotic and antidepressants may inhibit MEGX formation due to depression of CYP450 isoenzyme while other drugs may enhance MEGX production.

## 22.4 Conclusion for Static and Dynamic Testing

Monitoring 'liver function' poses significant problems regarding the diverse parenchymal metabolites. As such, quick and accurate assessment of global liver function in the critically ill patients is difficult, and the conventional static measures (i.e. bilirubin and transaminases) are too sluggish to meet this demand.

In the end, excretory function of the liver is the essence of monitoring impairments in liver function in critically ill patients, in the absence or presence of pre-existing liver disease. Currently its assessment is best measured by MELD and bilirubin in the cirrhotic patient and by quantitative test of ICG-PDR or MEGX, in absence of liver disease. Both ICG-PDR and MEGX tests are clinically most accurate and reproducible, however, ICG-PDR has advantage of being measurable noninvasively at bedside and providing result within minutes.

## References

1. Guyton and Hall Textbook of Medical Physiology, 12th edition, Chapter 70, The Liver as an Organ; 881–886. Saunders Elsevier 2011

2. Paxian M, Bauer I, Rensing H, et al. Recovery of hepatocellular ATP and pericentral apoptosis after hemorrhage and resuscitation. *FASEB J*. 2003;17:993–1002.
3. Oellerich M, Burdelski M, Lautz HU, et al. Assessment of pre-transplant prognosis in patients with cirrhosis. *Transplantation*. 1991;51:801–6.
4. Reichling JJ, Kaplan MM. Clinical use of serum enzyme in liver diseases. *Dig Dis Sci*. 1988;33:1601–14.
5. Sakka SG. Assessing liver function. *Curr Opin Crit Care*. 2007;13:207–14.
6. Hoekstra LT, de Graaf W, Nibourg GAA, Heger M, Bennink RJ, Stieger B, van Gulik TM. Physiological and biochemical basis of clinical liver function tests: a review. *Ann Surg*. 2013;257:27–36.
7. Faybik P, Hetz H. Plasma disappearance rate of indocyanine green in liver dysfunction. *Transplant Proc*. 2006;38:801–2.
8. Faybik P, Krenn C-G, Baker A, Lahner D, Berlakovich G, Steltzer H, Hetz H. Comparison of invasive and noninvasive measurement of plasma disappearance rate of indocyanine green in patients undergoing liver transplantation: a prospective investigator-blinded study. *Liver Transpl*. 2004;10:1060–4.
9. Sakka SG, Koeck H, Meier-Hellmann A. Measurement of indocyanine green disappearance rate by two different dosages. *Intensive Care Med*. 2004;30:506–9.
10. <http://www.drugs.com/drug/indocyanine-green.html>.
11. Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of invasive and non invasive measurements of ICG-PDR in critically ill patients with mechanical ventilation and stable hemodynamics. *Intensive Care Med*. 2000;26:1553–6.
12. Vos JJ, Scheeren TWL, Lukes DJ, de Boer MT, Hendriks HGD, Wietasch JKG. Intraoperative ICG plasma disappearance rate helps to predict early post-operative complications after orthotopic liver transplantation. *J Clin Monit Comput*. 2013;27:591–8.
13. Kortgen A, Pixian M, Werth M, Recknagel P, Rauchfuss F, Lupp A, Krenn CG, Muller D, Claus RA, Reinhart K, Settmacher U, Bauer M. Prospective assessment of hepatic function and mechanisms of dysfunction in critically ill. *Shock*. 2009;32:358–65.
14. Babb RR, McPherson JR. The sulfobromophthalein sodium test: a review. *Manit Med Rev*. 1966;46:124–6.
15. Oellerich M, Armstrong VW. The MEGX test: a tool for real time assessment of hepatic function. *Ther Drug Monit*. 2001;23:81–92.
16. Schroter J, Wandel C, Bohrer H. Lignocaine metabolite formation: an indicator of liver dysfunction and predictor of survival in surgical intensive care patients. *Anaesthesia*. 1995;50:850–4.
17. Maynard ND, Bihari DJ, Dalton RN, et al. Liver function and splanchnic ischemia in critically ill patients. *Chest*. 1997;111:180–7.

# Index

## A

- Abdominal compartment syndrome (ACS), 130, 131, 143, 247
  - definition, 131
  - diagnosis, 132
  - management, 133
  - normal IAP to IAH to ACS spectrum, 131, 132
- Acetaminophen (APAP), 214
- Acetaminophen nephrotoxicity, 53
- Acetaminophen toxicity, 76
- Acetaminophen-induced ALF, 76
- ACLF Acute on chronic liver failure (ACLF)
  - Acute and chronic liver disease
    - clinical background, 179–180
    - estimation of needs, 182
    - malnutrition, 180–181
    - metabolic syndrome, 180
    - micronutrient, 182–183
    - nutrition assessment, 181
    - nutrition delivery
      - branched chain amino acids, 184
      - enteral nutrition, 183
      - oral diet, 183
      - parenteral nutrition, 183, 184
    - nutrition screening tools, 181
  - organ transplant, 186
  - protein dose and formulation, 184
  - sarcopenia
    - aerobic and resistance activity, 185
    - Child-Pugh, 185
    - D'Amico stage classification, 185
    - leucine-rich supplements, 185
    - and liver transplant, 186
    - mechanisms, 185
    - MELD scores, 185
    - vs. non-sarcopenic group, 185
    - obesity, 185
    - therapeutic options, 185
    - transjugular intrahepatic portosystemic shunt, 185
- Acute kidney injury (AKI)
  - ACLF, 153, 158, 159
  - ADQI workgroup, 156
  - AKIN criteria, 156
  - assessment
    - cystatin C, 154–155
    - GFR, 155
    - methods, 155
    - sCr, 154
  - in cirrhosis
    - biomarkers, 156–157
    - diagnostic criteria, 156
    - inflammation, 154
  - epidemiology, 154
  - HRS Hepatorenal syndrome (HRS), AKI
  - KDIGO, 156
  - pre and post transplant history, 159
  - RIFLE criteria, 156
  - treatment, 159
- Acute liver failure (ALF), 37, 41
  - acetaminophen toxicity, 76
  - ACLF Acute on chronic liver failure (ACLF)
  - acute-on-chronic liver failure, 75
  - artificial ECLS systems, 293
  - bacterial infections, 198–199
  - bioartificial ECLS systems, 293, 296
  - cardiac dysfunction, 107–109
  - cardiovascular
    - antiarrhythmics, 218
    - cirrhotic cardiomyopathy, 217
    - vasopressors, 217–218
  - causes, 46, 292
  - vs. chronic liver disease, 75
  - cirrhosis, 76
  - clinical features, 164, 172
  - CRRT, 224
  - definition, 292
  - ECLS systems Extracorporeal liver support (ECLS) systems
  - ECMO, 225, 226
  - endocrine
    - adrenal insufficiency, 224
    - glycemic control, 223
    - thyroid, 223
  - etiology, 46, 76
  - gastrointestinal Gastrointestinal disease
  - hematology
    - autoanticoagulation, 221
    - HIT, 221–222
  - hemostatic abnormalities, 175–176
  - hepatic encephalopathy
    - brain imaging, IH, 95–97
    - cerebral edema and mortality, 84
    - clinical and laboratory assessment, 95
    - management outline, 96–99
    - neuro checks, 95
    - neuroprotective strategies, 99–100
    - noninvasive neuromonitoring strategy, 99
    - plasma ammonia lowering strategies, 100
    - risk factor, 95
    - serial laboratory testing objectives, 95
  - hepatocellular dysfunction, 46
  - hypercoagulable state, 175
  - infectious disease, 221–223
  - King's college criteria, 76
  - liver transplantation, 292
  - management, 280, 284

- Acute liver failure (ALF) (*cont.*)
  - management strategies, 292
  - MARS, 294
  - MELD, 76
  - multi-organ failure, 46
  - neurologic Neurology
  - pharmacodynamics
    - absorption, 212
    - distribution, 212
    - elimination, 212
    - metabolism, 212–213
  - pharmacokinetics
    - absorption, 212
    - distribution, 212
    - elimination, 212
    - intrinsic hepatic drug clearance, 213
    - metabolism, 212
  - prognosis, 76
  - pulmonary
    - endothelin receptor antagonists, 219–220
    - phosphodiesterase inhibitors, 219
    - synthetic prostacyclins, 218
  - rebalanced hemostasis, 168
    - maximum blood clot strength, 173
    - microparticles, 174
    - MPTF, 174, 175
    - platelet aggregation, 173
    - thromboelastography, 172, 173
    - whole blood clot lysis, 175
  - renal, 220
  - toxin accumulation, 292
  - vonWillebrand factor (vWF), 167
- Acute on chronic liver failure (ACLF), 80, 84
  - acute deterioration, 292
  - AKI, 153, 158, 159
  - artificial ECLS systems, 293
  - bioartificial ECLS systems, 293
  - cardiovascular
    - antiarrhythmics, 218
    - vasopressors, 217
  - CLIF-SOFA score, 292
  - CRRT, 224
  - decompensated cirrhosis, 46
  - definition, 292
  - diagnostic criteria, 46
  - ECLS systems Extracorporeal liver support (ECLS) systems
  - ECMO, 225, 226
  - endocrine
    - adrenal insufficiency, 224
    - glycemic control, 223
    - thyroid, 223
  - gastrointestinal Gastrointestinal disease
  - hematology
    - autoanticoagulation, 221
    - HIT, 221
  - hemodynamic abnormalities, 47
  - infectious disease, 222–223
  - inflammatory markers, 47
  - liver transplantation, 292
  - MARS, 293
  - multi-organ failure, 47
  - neurologic Neurology
  - NGAL, 47
  - pharmacodynamics
    - absorption, 212
    - distribution, 212
    - elimination, 212
    - metabolism, 212
  - pharmacokinetics
    - absorption, 212
    - distribution, 212
    - elimination, 212
    - intrinsic hepatic drug clearance, 213
    - metabolism, 212
  - potential biomarkers, 47
  - precipitating events, 46
  - pulmonary
    - endothelin receptor antagonists, 219–220
    - phosphodiesterase inhibitors, 219
    - synthetic prostacyclins, 218–219
  - renal, 220
  - SIRS, 47
  - toxin accumulation, 292
- Acute physiology and chronic health evaluation (APACHE), 202
- Acute respiratory distress syndrome (ARDS), 277
  - ACURASYS trial, 40, 41
  - ARDSNet protocol, 41
  - ARDSNet trial, 40
  - Childs-Pugh class C alcoholic cirrhosis, 40
  - extrapulmonary consequences, 41
  - lung-protective ventilation, 41
  - neuromuscular blockade, 40, 41
  - optimal ventilator management, 41
  - paracentesis, 41
  - PEEP, 41
  - proning, 41
- Acute Respiratory Distress Syndrome Network (ARDSNet) protocol, 41
- Adrenal insufficiency, 224
- Advanced liver disease
  - clinical implications
    - ACLF, 80
    - compensated disease, 79
    - decompensated disease, 79
    - hepatocellular carcinoma, 80
    - non-alcoholic liver disease, 81
  - epidemiology, 78–79
- AKI Acute kidney injury (AKI)
- Alanine transferase (ALT), 11, 12
- Albumin, 8, 12
- Albumin hypothesis, 293
- ALF Acute liver failure (ALF)
- Alkaline phosphatase (ALP), 11, 12
- $\alpha_1$ -antitrypsin gene, 8
- Alveolar macrophages, 139
- Ambrisentan, 220
- American Association for the Study of Liver Diseases (AASLD), 46
- American Association for the Surgery of Trauma (AAST) Organ Injury Scale, 241
- American Society of Anesthesiologists (ASA) monitors, 271
- Amino acid metabolism, 8
- Aminopyrine test, 16
- Aminotransferases, 11
- Amiodarone, 218
- Ammonia, 8, 13
- Ammonia scavengers, 94
- Analgesics
  - acetaminophen, 214
  - anticonvulsants, 215
  - monitoring, 214
  - NSAID, 215
  - opioids, 214



- tramadol, 215
  - tricyclic antidepressants, 215
  - Angioembolization, 246
  - Antiarrhythmics, 218
  - Anti-coagulation factors, 8
  - Anticonvulsants, 215
  - Antidiuretic hormone (ADH), 55, 125
  - Anti-emetics
    - metoclopramide, 221
    - ondansetron, 221
  - Antiepileptic drug (AED) therapy, 216
  - APCHE II score, 302
  - Aquaporins, 55
  - Argatroban, 222
  - Arginine vasopressin Antidiuretic hormone
  - Arterial hypoxemia, 138
  - Artificial ECLS systems
    - ACLF, 293
    - adverse effect profile, 295–296
    - ALF, 293
    - detoxification, 293
  - Artificial systems, 224
  - Ascites
    - abdominal compartment syndrome, 143
    - complications, 143
    - hepatorenal syndrome, 50
    - HRS, 154
    - IAH Intraabdominal hypertension (IAH)
    - IAP, 143
      - large volume paracentesis, 144
      - nasogastric stomach decompression, 144
      - surgical methods, 144
    - IAV, 143, 144
    - mechanical ventilation, 144
    - neuromuscular blockers, 144
    - NIPPV, 144
    - pathogenesis, 49
    - porto-pulmonary hypertension, 144
    - renal vasoconstriction system, 50
    - SBP, 49
    - sedation, 144
    - sympathetic nervous system, 50
    - TIPS, 261
  - Asian Pacific Association for the Study of the Liver (APASL), 46
  - Aspartate transferase (AST), 11, 12
  - Atrial arrhythmias, 279
  - Atrial fibrillation, 279
  - Atrial natriuretic peptide (ANP), 111
  - Autoanticoagulation, 169, 221
  - Autoimmune disease, 78
  - Autoimmune hepatitis, 78
- B**
- Bacterial infections
    - ALF, 198
    - bloodstream infections, 195
    - CDAD, 196
    - Clostridium Difficile* infection, 196
    - endotipsitis, 195
    - pathophysiology, 191–192
    - pneumonia, 195
    - SBP
      - antibiotic prophylaxis, 194
      - cirrhotic ascites, 192
      - definition, 192
      - diagnosis, 193–194
      - management, 194
      - mechanism of infection, 192
      - microbiology, 192–193
      - presentation, 192
      - prevention, 194–195
      - risk factors, 192
    - SSTIs, 195
    - urinary tract infections, 195
  - Balloon tamponade, 126
  - Balloon-occluded retrograde transvenous obliteration (BRTO), 126
  - Barbiturate coma, 100
  - Behavioral Pain Scale (BPS), 214
  - Benzodiazepine, 216, 273
  - $\beta$ -adrenergic system, 27, 28
  - Beta-adrenoreceptor antagonists, 217
  - Beta blockers/ $\beta$ -blockers Beta-adrenoreceptor antagonists
  - $\beta$  globulins, 8
  - Bile acid synthesis, 8
  - Bile acids, 8, 9, 13
  - Bile cast nephropathy, 57
  - Bile leak
    - and biloma formation, 239
    - diagnosis, 239
    - ERCP, 239
    - grade A, 239
    - grade B, 239
    - grade C, 239
    - ISGLS, 239
    - management, 239
    - mortality, 239
    - MRCP, 239
  - Bile salts, 9
  - Biliary system, 6
  - Bilirubin, 11–13
  - Bioartificial ECLS (B-ECLS) systems
    - ACLF, 293
    - albumin hypothesis, 293
    - ALF, 293, 296, 297
    - design, 296
  - Bioartificial system, 224
  - Biphasic positive airway pressure (BiPAP), 277
  - Blood and blood product transfusions, 167–169
  - Blood flow
    - cholestasis, 203
    - estimation, 202
    - hepatic cellular architecture, 203
    - hepatic ischemia and hypoxia, 203
    - hypoxic hepatitis, 203
    - lobular architecture, 203
    - lung and liver, 202
    - occult liver disease and dysfunction impact, 203
  - Bloodstream infections, 195
  - Blunt liver injuries (BLI), 240
  - Bosentan, 219
  - Brain natriuretic peptide (BNP), 26
  - Branched chain amino acids (BCAA), 92–95, 184
  - Bromosulphophthalein clearance (BSP) test, 16, 302
  - B-type natriuretic peptide (BNP), 111
  - Budd-Chiari syndrome, 261
- C**
- C. difficile* associated diarrhea (CDAD), 196
  - Caffeine test, 16, 302
  - Calcium channel blocker, 218

- Carbohydrate metabolism, 299
- Carbon monoxide (CO), 27, 28
- Cardiac cirrhosis
  - cardiac systolic changes, 23–24
  - characteristics, 22
  - congestive hepatopathy, 22
  - diastolic changes
    - cardiac hypertrophy, 26
    - diastasis period, 25
    - diastolic filling, 25
    - pressures and filling rates, 25
    - sarcoplasmic reticulum, 25
    - systolic and diastolic contractile dysfunction, 26
    - tissue Doppler imaging, 26
    - ventricular diastole, 25
  - electrophysiologic abnormalities, 26
  - fluid volume regulation, 23, 24
  - histological changes, 23
  - impaired cardiovascular responsiveness, 23
  - left ventricular hypertrophy, 26
  - recognition and diagnosis, 22
  - stress testing, 23
  - volume redistribution, 23
- Cardiac disease
  - cardiac dysfunction, 208
  - ischemic hepatitis, 207–208
  - passive congestion, 206
- Cardiac dysfunction
  - alcoholic cardiomyopathy, 109
  - ALF, 107
  - biomarkers, 111
  - cardiac cirrhosis, 106, 109, 110
  - cardiac imaging
    - cardiac stress testing, 112
    - CMR imaging, 112
    - Doppler echocardiography, 111–112
  - chronic liver failure, 109
  - chronotropic incompetence, 110
  - cirrhotic cardiomyopathy, 106, 109, 110
  - diagnosis
    - acute ischemic hepatitis vs. cardiac cirrhosis, 111
    - clinical symptoms, 110
    - E/A ratio, 110
    - hydrothorax, 110
    - laboratory evaluation, 111
    - systolic and diastolic function, 110
  - electrophysiological abnormalities, 110
  - intensive care unit evaluation
    - ACLF diagnosis, 113
    - acute decompensation, 112, 113
    - adrenal insufficiency, 114
    - albumin, 114
    - circulatory shock hemodynamic monitoring, 113
    - corticosteroids, 114
    - CVP, 113–114
    - echocardiography, 113
    - hemodynamic assessment, 113
    - hemodynamic collapse, 113
    - hemodynamic variables, shock, 113
    - organ failure and mortality, 113
    - prognostic scoring systems, 113
    - RAAS activation, 113
    - resuscitative efforts, 113
    - terlipressin, 114
    - vasopressin, 114
  - ischemic hepatitis, 106
  - liver transplantation
    - cardiac catheterization, 115
    - myocardial dysfunction, 115
    - pharmacologic stress test, 115
    - portopulmonary HTN, 115
    - post-operative heart failure, 115
    - post-transplant reperfusion, 115
    - systemic hypertension, 115
  - portal hypertension, 114
  - pulmonary HTN, 114–115
  - QT prolongation abnormalities, 110
  - TIPS, 114
- Cardiac magnetic resonance (CMR) imaging, 112
- Cardiac troponin I and T (cTnT), 111
- Cardiovascular disease
  - antiarrhythmics, 218
  - vasopressors, 217
- L-Carnitine, 92–95
- Catecholamines, 27, 217
- Cavernoma, 126, 127
- Cell saver autotransfusion, 271
- Central venous pressure (CVP), 29
- Cerebral edema, 280
- Ceruloplasmin, 8
- Child-Pugh score, 15, 34, 235
  - class A and B cirrhosis, 34
- Child Turcotte Pugh score, 202, 256
- Cholecystectomy
  - perioperative management, 263
  - preoperative assessment, 263
- Cholestasis, 213
- Cholesterol, 7
- Chronic liver disease
  - vs. acute liver failure, 75
  - cardiac dysfunction, 109
  - chronic pathologic processes, 77
  - cirrhosis
    - blood and blood product transfusions, 165–169
    - destabilization, 171–172
    - hypercoagulable state Hypercoagulable state
    - rebalanced hemostasis, 165–168
  - hepatic encephalopathy
    - chronic ammonia exposure, 86
    - clinical features, 88
    - goals of therapy, 92
  - hepatic stellate cell activation, 77
  - multisystem organ failure, 77
  - progressive fibrosis, 77
- Chronic Liver Failure Organ Failure (CLIF) score, 113
- Chronotropic incompetence, 110
- Circulatory physiology
  - cardiovascular response
    - $\beta$ -adrenergic system, 27
    - carbon monoxide, 27, 28
    - EDHF, 28
    - endogenous cannabinoids, 27, 28
    - prostacyclin, 28
    - TNF- $\alpha$ , 28
  - circulatory dysfunction, clinical impact, 28–29
  - cirrhotic cardiomyopathy Cirrhotic cardiomyopathy
  - hyperdynamic circulation, 21
  - portal hypertension Portal hypertension
  - splanchnic circulation, 21, 22
  - systemic circulation, 21, 22
- Cirrhosis
  - alcohol related disease, 78

- autoimmune disease, 78
  - chronic liver disease, 168–170
    - blood and blood product transfusions, 167–169
    - destabilization, 171–172
    - hypercoagulable state Hypercoagulable state
    - rebalanced hemostasis, 165–168
  - chronic liver failure, 109
  - clinical features, 164
  - metabolic disease, 78
  - NAFLD, 78
  - transfusion, 262
  - viral disease, 77
  - Cirrhosis vonWillebrand factor (vWF), 167
  - Cirrhosis-associated immunodeficiency (CAID), 192
  - Cirrhotic cardiomyopathy
    - alcoholic cardiomyopathy, 22
    - altered diastolic relaxation, 106
    - blunted cardiac response to stress, 109
    - cardiac decompensation, 28
    - cardiac hemodynamics, 28
    - characteristics, 22, 23, 54
    - diagnostic and supportive criteria, 106
    - diastolic dysfunction, 110
    - electrophysiological abnormalities, 106
    - hepatorenal syndrome, 109
    - high output heart failure, 106
    - natriuretic peptides, 26
    - non-alcoholic cirrhotic patients, 22
    - symptoms, 106
  - Clostridium Difficile* infection (CDI), 196
  - Coagulation management, 258, 282
  - Complement components (C3), 8
  - Composite score, 256
  - Continuous positive airway pressure (CPAP), 277
  - Continuous renal replacement therapy (CRRT), 93, 100, 224, 280
  - Contrast-enhanced transthoracic echocardiogram (CTTE), 141
  - Critical illness
    - adrenal function, 206
    - antioxidant vitamin C functions, 205
    - bilirubin reflect, 202
    - blood flow
      - cholestasis, 203
      - estimation, 202
      - hepatic cellular architecture, 202, 203
      - hepatic compliance, 203
      - hepatic ischemia and hypoxia, 203
      - hepatocellular function, 203
      - hypoxic hepatitis, 203
      - lobular architecture, 203
      - lung and liver, 202
      - occult liver disease and dysfunction impact, 203
    - cardiac disease
      - cardiac dysfunction, 208
      - ischemic hepatitis, 206–208
      - passive congestion, 206–207
    - functional liver studies, 202
    - hepatic immune function, 202
    - hepatocyte toxicity, 206
    - IIT, 206
    - liver function reflect, 201
    - liver support devices, 206
    - MEGX formation, 202
    - prothrombin time/factor V levels, 202
    - scoring systems, 202
    - sepsis
      - definition, 204
      - hepatocellular events, 204
      - injury pattern, 205
      - mortality, 204
      - organ dysfunction and failure, 204
      - survivors and non-survivors, 202
  - Critical-Care Pain Observation Tool (CPOT), 214
  - Cyclic AMP, 27
  - Cystatin C, 155
  - Cytosolic function, 202
- ## D
- Damage associated molecular patten (DAMP), 154
  - Damage control surgery (DCS), 245
  - Deep venous thrombosis (DVT), 244
  - Dexmedetomidine, 216, 273
  - Diagnostic peritoneal lavage (DPL), 240
  - Diastolic dysfunction, 110–115
  - Diffusion capacity of carbon monoxide (DLCO), 38
  - Diltiazem, 218
  - Distal renal tubular acidosis, 57
  - Dobutamine, 112
  - Dobutamine stress echocardiography (DSE), 278
  - Dubin-Johnson syndrome, 16
  - Dynamic tests
    - bromosulfophthalein clearance, 302
    - caffeine, 302
    - ICG Clearance, 301–302
    - MEGX, 302
- ## E
- Electrocardiogram (ECG), 273
  - Electrolyte abnormality, 238
  - Endocannabinoids Endogenous cannabinoids (EC)
  - Endocrine disease
    - adrenal insufficiency, 224
    - glycemic control, 223
    - thyroid, 223
  - Endogenous cannabinoids (EC), 27, 28
  - Endoscopic procedures, 263
  - Endoscopic variceal band ligation (EVL), 125
  - Endoscopic variceal sclerotherapy (EVS), 125
  - Endothelial nitric oxide synthase (eNOS), 47, 140
  - Endothelin (ET)-1, 140
  - Endothelin receptor antagonists, 219–220
  - Endothelium-derived hyperpolarizing factor (EDHF), 28
  - Endotipsitis, 195
  - End-stage liver disease (ESLD), 139
    - alcohol consumption, 257
    - cholecystectomy
      - latent cirrhosis, 263
      - perioperative management, 263
      - preoperative assessment, 263
    - endoscopic procedures, 263–264
    - hepatic function, 257
    - intraoperative management
      - anesthetics effect, 260
      - atracurium, 259
      - benzodiazepines, 259
      - choice of monitors, 258
      - cisatracurium, 259
      - coagulation management, 258–259
      - meperidine, 259
      - metabolite normeperidine, 259
      - neuraxial anesthesia, 260

- End-stage liver disease (ESLD) (*cont.*)  
  neuromuscular blocking agents, 259  
  opioids, 259  
  succinylcholine metabolism, 259  
  vasopressin, 260  
  volume resuscitation, 260  
  intravascular volume management, 262  
  laboratory evaluation, 257  
  liver enzymes, 257  
  medications, 257  
  physical examination findings, 257  
  postoperative care, 262–263  
  preoperative optimization, 257–258  
  preoperative risk stratification  
    acute hepatitis, 257  
    Child–Turcotte–Pugh score, 256  
    cirrhosis, 256  
    composite score, 256  
    diagnostic testing, 257  
    MELD score, 256  
    prognostic factors, 256  
    umbilical hernias, 256  
  preprocedure evaluation  
    cardiac considerations, 261–262  
    coagulation, 261  
    hemostasis considerations, 262  
    right heart function, 261  
    right ventricular systolic pressure, 261  
  symptoms, 257  
  TIPS  
    ascites, 261  
    contraindications, 256  
    MELD score, 261  
    portal decompression, 261  
    systematic workup, 261  
  Enteral nutrition (EN), 183  
  Epidural analgesia, 284  
  Epoprostenol, 218  
  Esomeprazole, 220  
  Esophageal varices (EV), 122  
  Esophagogastroduodenoscopy (EGD), 263  
  Extracorporeal albumin dialysis, 158–159  
  Extracorporeal Liver Assist Device (ELAD), 225  
  Extracorporeal liver support (ECLS) systems  
    ALF Acute liver failure (ALF)  
      artificial, 224  
      ACLF, 293  
      adverse effect profile, 295–296  
      albumin hypothesis, 293  
      ALF, 293  
      detoxification, 293  
    bioartificial, 224  
      ACLF, 293  
      ALF, 293, 296  
      design, 296  
    ceftazidime, 225  
    ceftriaxone, 225  
    FPSA, 295  
    hepatic functions, 292  
    HVP, 295  
    levofloxacin, 225  
  MARS  
    albumin circuit, 293  
    ALF, 294  
    blood circuit, 293  
    classic “renal” circuit, 293  
    inflammatory profile, 294  
    meropenem, 225  
    moxifloxacin, 225  
    piperacillin-tazobactam, 225  
    SPAD, 295  
    tacrolimus, 225  
    teicoplanin, 225  
  Extracorporeal membrane oxygenation (ECMO), 225, 226
- F**  
  Fat metabolism, 300  
  Ferritin, 8  
  Fibrinogen, 258, 259  
  Fibrinogen concentrates (FC), 259  
  Fibrinolysis, 242  
  Flumazenil, 94  
  Fractionated plasma separation and adsorption (FPSA), 295  
  Fresh frozen plasma (FFP), 245, 249, 259, 282  
  Future Liver Remnant (FLR)  
    CT volumetry, 236  
    kinetic growth rate, 236  
    management, 236  
    portal vein embolization, 236  
    post-operative liver function, 236  
    validation formula, 236
- G**  
  Galactose tolerance tests, 7  
  Gallstones, 9, 256, 257, 263  
  Gamma glutamyl transferase ( $\gamma$ -GT), 11, 13  
   $\gamma$  globins, 8  
  Gastro-esophageal variceal hemorrhages, 220  
  Gastrointestinal disease  
    anti-emetics  
      metoclopramide, 221  
      ondansetron, 221  
    histamine-2 receptor antagonists, 221  
    proton pump inhibitors  
      esomeprazole, 220  
      lansoprazole, 220  
      omeprazole, 220  
      pantoprazole, 220  
  Glisson’s capsule, 4  
  Glomerular filtration rate (GFR), 154–156  
  Glutathione (GSH), 139  
  Glycemic control, 223, 281
- H**  
  Hematology  
    autoanticoagulation, 221  
    HIT, 221  
  Hemochromatosis, 78  
  Hemorrhage, 283  
  Hemostasis, 295  
  Heparin-induced thrombocytopenia (HIT), 221  
  Hepatic blood flow, 213  
  Hepatic encephalopathy (HE), 46, 56, 92, 125, 261  
    ALF Acute liver failure (ALF), hepatic encephalopathy  
    chronic liver disease  
      chronic ammonia exposure, 86  
      clinical features, 88  
      goals of therapy, 92  
    classification and grading, 83, 84



- neurological assessment
  - asterixis grading, 88, 89
  - Confusion Assessment Method, 88
  - Glasgow Coma Scale, 88, 89
  - RASS, 88
- pathophysiology
  - ammonia, 85–88
  - cerebral astrocytes, 86
  - cytotoxic edema, 86
  - glutamine, 85–87
  - hyperammonemia, 85, 88
  - hyperemia, 86, 88
  - hyponatremia, 86
  - intracranial hypertension, 86
  - intraluminal ammonia, 87
  - malignant cerebral edema, 86
  - vasogenic edema, 86
- physical exam, 89
- type C Type C HE
- West Heaven criteria, 84
- Hepatic hydrothorax (HH), 141
  - absence of ascites, 142
  - case examination, 141
  - characteristic features, 142, 147
  - chest radiography, 142
  - pathophysiology, 141–142
  - pleural effusions, 142
  - pleuroperitoneal communications, 142
  - symptoms, 142
  - thoracentesis, 142
  - transudative pleural effusion, 141
  - treatment
    - dietary sodium restriction, 142
    - diuretic agents, 142
    - fluid mobilization, 142
    - liver transplantation, 142
    - peritoneovenous shunting, 142
    - therapeutic thoracentesis, 142
    - TIPS, 142
    - video assisted thoracoscopic surgery with pleurodesis, 142
- Hepatic insufficiency, 237
- Hepatic necrosis, 246
- Hepatic sinusoids, 46
- Hepatic stellate cells, 47
- Hepatic surgery
  - bile leak, 239
  - biloma formation, 239
  - Couinaud hepatic segmental anatomy, 236, 237
  - electrolyte abnormality, 238
  - hepatic insufficiency/failure, 239
  - intrahepatic arterial anatomy, 236
  - intrahepatic biliary anatomy, 236
  - intra-operative transfusion, 238
  - laparoscopic and robotic surgery, 234
  - liver resection, 234, 236
  - post-hepatectomy hemorrhage
    - bleeding, 238
    - clinical examination, 238
    - grade A, 238
    - grade B, 238
    - grade C, 238
    - hemorrhage control, 238
    - incidence, 238
    - ISGLS, 238
    - patient factors, 238
    - resuscitation, 238
  - standard coagulation tests, 238
  - TEG, 238
  - postoperative management, 237, 238
  - preoperative planning
    - Child-Pugh score, 235
    - FLR, 236
    - lesion respectability, 235
    - MELD score, 235
    - patient operability, 234–235
  - surgical anatomy, 236
  - treatment modality, 234
  - venous outflow, 236
- Hepatic trauma
  - AAST liver organ injury scale, 241
  - angiography, 246
  - BLI, 240
  - in cirrhosis, 244
  - clinical background, 240
  - complications, 246
    - abscesses, 247
    - ACS, 247
    - angioembolization, 246
    - bile peritonitis, 247
    - biliary, 246, 247
    - bleeding, 246, 247
    - infectious, 246
  - contrast extravasation, 245, 246
  - DPL, 240
  - embolization, 246
  - grading system, 241
  - LFT, 241
  - NOM
    - advantages, 243
    - altered mental status, 243
    - management, 243, 244
    - mortality, 242
    - outcomes, 243–244
    - Ruscitation Outcomes Consortium, 243
    - solid organ injury, 242
  - non-operative and operative, 240
  - operative management, 244–245
  - outcomes, 240
  - resuscitation, 241–242
  - VTE, 244–245
- Hepatic vein pressure gradient (HPVG), 48
- Hepatic venous pressure gradient (HVPG)
  - upper normal value, 121
  - variceal bleeding, 121
- Hepatitis A virus (HAV), 196
- Hepatitis B virus (HBV), 77, 197
- Hepatitis C virus (HCV), 77, 197
- Hepatitis D virus (HDV), 197
- Hepatitis E virus (HEV), 197
- Hepatoadrenal syndrome Relative adrenal insufficiency (RAI)
- Hepatocellular carcinoma (HCC), 80, 126
- Hepatocellular synthetic function, 301
- Hepatocytes, 139
- Hepatofugal flow, 48
- Hepatopulmonary syndrome (HPS), 38, 141, 144, 202, 257, 262, 278
  - abnormal communications, 140
  - abnormal dilatation, 140
  - arterial hypoxemia mechanisms, 138
  - classification, 140
  - clinical manifestations, 140–141
  - diagnosis
    - angiography, 141

- Hepatopulmonary syndrome (HPS) (*cont.*)
    - impaired arterial gas exchange, 141
    - IPVD detection, 141
    - MAA scan, 141
    - pulmonary vascular dilatation, 141
    - fixed pulmonary vascular tone, 140
    - IPVD mechanisms, 140, 147
    - nitric oxide, 140
    - treatment, 141
    - triad, 140
  - Hepatorenal syndrome (HRS), AKI, 50, 157, 158, 194, 213, 216, 261, 280
    - ascites, 154
    - circulatory dysfunction and, 154
    - clinical manifestations, 154
    - irreversibility, 153
    - renal vasoconstriction, 153
    - sCr, 154
    - sodium retention, 154
    - splanchnic vasodilatation, 153
    - therapies
      - albumin, 157
      - extracorporeal liver support, 158
      - liver transplantation, 157
      - RRT, 158
      - TIPS, 158
      - vasoconstrictor therapies, 157–158
    - type 1 and 2, 154, 156
  - Hepatotoxin Acetaminophen
  - High-volume plasmapheresis (HVP), 224, 295
  - Histamine-2 receptor antagonists, 221
  - HRS, 220 Hepatorenal syndrome (HRS)
  - Human immunodeficiency virus (HIV), 197–198
  - Hypercoagulable state, 127
    - ALF, 175
    - chronic liver disease
      - anticoagulation effect, 170, 171
      - autoanticoagulation, 169
      - bleeding tendency, 168
      - clinical observations, 169
      - continuous renal replacement therapy, 169
      - etiologies, 169
      - mechanisms, 169
      - NASH, 169
      - portal and hepatic venous micro-obliterative lesions, 168
      - PVT, 169, 170
      - venous thromboembolism, 169, 171
  - Hyperdynamic circulation, 48
  - Hyperkalemia, 280
  - Hyperlactemia, 238
  - Hyperosmotic agents, 99–100
  - Hypertension, 279
  - Hypertonic saline, 99
  - Hyperventilation, 100
  - Hypervolemic/dilutional hyponatremia, 55, 56
  - Hypoalbuminemia, 49
  - Hypokalemia, 125
  - Hyponatremia, 56, 99
  - Hypophosphatemia, 125, 238
  - Hypothermia, 100
  - Hypothesized neurotoxic mechanisms, 85
  - Hypoxia mechanisms Hypoxic respiratory failure
  - Hypoxic hepatitis Ischemic hepatitis
  - Hypoxic pulmonary vasoconstriction, 138
  - Hypoxic respiratory failure
    - ARDS and liver disease, 139
    - arterial hypoxemia mechanisms, 138
    - case examination, 137
    - diffusion impairment, 139
    - 2, 3-diphosphoglycerate, 138
    - gas exchange abnormalities, 138
    - hypoventilation, 138
    - hypoxic pulmonary vasoconstriction, 138
    - intrapulmonary shunting, 138–139
    - intrapulmonary vascular dilatation, 138
    - lung protection, role of liver, 139
    - premature airway closure, 138–139
    - pressure of oxygen (PaO<sub>2</sub>), 138
    - V/Q mismatch, 138
- ## I
- IAH Intraabdominal hypertension (IAH)
  - Immunoglobulins, 8
  - Immunosuppression, 282–283
  - Impaired synthetic function, 46
  - Indocyanine green (ICG) clearance test, 16, 301
  - Indocyanine Green-plasma disappearance rate (ICG-PDR)
    - APACHE II score, 302
    - gold standard technique, 301
    - limitations, 302
    - MOD, 302
    - SOFA, 302
    - spectrophotometric analysis, 301
  - Indomethacin, 100
  - Inducible nitric oxide synthase (iNOS), 140
  - Infectious disease, 222–223
  - Intensive insulin therapy (IIT), 206
  - Interleukin-18, 157
  - International Study Group on Liver Surgery (ISGLS), 238, 239
  - Intraabdominal hypertension (IAH), 57, 130
    - ACS Abdominal compartment syndrome (ACS)
      - categorizations, 131, 132
      - definition, 130
      - effects on organ systems, 132
    - IAP, 131
    - management, 133–136
    - normal IAP to IAH to ACS spectrum, 131, 132
    - presentation and diagnosis, 132–133
    - risk factors, 132
    - wall compliance, 131
    - WSACS, 131
  - Intra-abdominal pressure (IAP), 131, 132
    - abdominal visceral function, 143
    - complications, 143–144
    - and IAV, 144
    - large volume paracentesis, 144
    - porto-pulmonary hypertension, 144
    - pulmonary mechanics, 143
    - surgical methods, 144
    - ventilator modes, 144
  - Intra-abdominal volume (IAV), 143, 144
  - Intracranial hypertension (IH)
    - ALF, 84
      - brain herniation, 95
      - brain MRI, 95, 97
      - intensive care supportive strategies, 96, 98
      - management outline, 96
      - risk factors, 95, 96, 98
      - serial laboratory testing objectives, 95
    - rare occurrence, 85
  - Intracranial pressure (ICP), 41, 84

Intrahepatic vascular resistance, 47  
 Intrahepatic vasoconstriction, 47  
 Intraoperative RRT, 159  
 Intravascular pulmonary vasodilatation (IPVD)  
   detection  
     angiography, 141  
     CTIE, 141  
   mechanisms, 140, 147  
 Intravenous iloprost, 218  
 Intrinsic positive end expiratory pressure (PEEP<sub>i</sub>), 36  
 Ischemic hepatitis, 111, 207, 208

## K

Ketoacidosis, 56  
 Kidney-injury molecule-1 (KIM-1), 157  
 Kinetic growth rate (KGR), 236  
 Krebs's cycle dysfunction, 8  
 Krebs-Henseleit cycle, 8  
 Kupffer cells (KC), 9, 10, 87, 139

## L

Lacosamide, 217  
 Lactic acidosis, 56  
 Lactic dehydrogenase (LDH), 11, 13  
 Lansoprazole, 220  
 Large esophageal varices, 49  
 Large volume paracentesis (LVP), 133  
 Left ventricular end diastolic pressure (LVEDP), 29  
 Levetiracetam, 217  
 Lipids, 7  
 Lipocalin-2 gene (LCN2), 27  
 Lipoproteins, 7  
 Liver  
   failure  
     cardiac cirrhosis, 107  
     concomitant congestive heart failure, 107  
     hyperdynamic circulation, 107, 108  
     hyperdynamic state, 107  
     ischemic hepatitis, 107  
     nitric oxide, 107  
     peripheral and splanchnic vasodilation, 107  
     systemic vasodilation, 107  
   function tests, 107  
   functional unit  
     hepatic lobule, 107  
     liver acinus, 107  
   reticuloendothelial system, 107  
 Liver anatomy  
   bile ducts, 6  
   blood flow, 6  
     deep networks, 5  
     hepatic artery, 4  
     hepatic veins, 4–5  
     lymphatic drainage, 5  
     lymphatic vessels, 6  
     portal and systemic circulation, 5  
     portal vein, 4  
     superficial networks, 5  
   falciparum ligament, 4  
   fibrous capsule, 4  
   fissures, 4  
   hepatoduodenal ligament, 4  
   porta hepatitis, 4  
   surgical/functional/segmental anatomy, 4, 5

  sympathetic and parasympathetic nerves, 6  
   weight, 4  
 Liver architecture  
   acinar module, 11  
   acinus nodule, 10  
   functional architecture, 11, 12  
   hepatocytes, 11  
   histological architecture, 11  
   lobule, 10  
   metabolic activity, 7, 11  
   sickle-cell shaped architecture, 11  
 Liver biopsy, 9  
 Liver disease  
   cardiac dysfunction Cardiac dysfunction  
   circulatory physiology Circulatory physiology  
   impaired hepatic synthetic function, 107  
   liver function tests, 107  
   lung volumes and capacities  
     ascites, 33, 34  
     chronic hepatitis, 34  
     closing volume, 34–35  
     concomitant liver disease, 34  
     FEV1/FVC ratio, 34  
     hepatic hydrothorax, 33  
     hepatic steatosis, 34  
     NAFLD, 33  
     obstructive defects, 34  
     pulmonary disease, 34  
     restrictive spirometric patterns, 34  
     small airway obstruction, 34–35  
     ventilatory defects, 33  
   renal physiology Renal physiology  
   respiratory physiology Respiratory physiology  
 Liver fibrosis, 77  
 Liver function  
   agents modulation, 3  
   bile synthesis and transport, 8  
   biliary system, 4  
   carbohydrate metabolism  
     disease, 7  
     functional heterogeneity, 7  
     glycogen synthesis, 7  
     lactate, 7  
   dynamic tests  
     bromosulphophthalein clearance, 302  
     caffeine, 302  
     ICG clearance, 301  
     MEGX, 302  
     pros, 301  
   immunological function, 9  
   LFTs, 241  
   lipid metabolism  
     diseases, 7  
     lipids, 7  
     lipoproteins, 7  
 NK cells, 9  
 nutrients extraction, 3  
 physiology  
   carbohydrate metabolism, 299  
   coagulation cascade, 300  
   fat metabolism, 300  
   hepatic macrophage system, 299  
   hepatic sinusoids, 299  
   liver lobule, 299, 300  
   protein metabolism, 300  
   storage site, 300

- Liver function (*cont.*)
    - protein synthesis, 8
    - static test
      - bilirubin, 300
      - enzymes, 301
      - hepatocellular synthetic function, 301
      - pros, 300
  - Liver histology
    - bile canaliculi, 10
    - endothelial cells, 10
    - hepatocytes, 10
    - macrophages, 10
    - microanatomy, 10
    - portal tracts, 9, 10
    - sinusoids, 10
    - stellate cells, 10
    - terminal hepatic venules, 10
  - Liver lobule, 299, 300
  - Liver resections
    - adjacent liver parenchyma, 234
    - anatomical, 236
    - indication, 234
    - mortality, 234
    - non-anatomical, 236
    - non-colorectal liver metastases, 234
    - treatment, 234
  - Liver sinusoidal endothelial cells (LSEC), 9
  - Liver tests
    - ammonia, 13
    - bile acids, 13
    - biochemical tests
      - ALP, 12
      - ALT, 12
      - aminotransferases, 11
      - assays, 11
      - AST, 12
      - bilirubin, 11
      - LDH, 11, 13
      - $\gamma$ -GT, 11, 13
    - clinical and biochemistry based scores, 15–16
    - dynamic, 16
      - amino acid clearance test, 16
      - aminopyrine, 16
      - bromosulphthalein, 16
      - caffeine test, 16
      - galactose elimination capacity, 16
      - indocyanine clearance green test, 16
      - rose Bengal test, 16
    - 5'NTD, 13
    - pattern and causes, 15
      - cholestatic pattern, 13
      - hepatocellular pattern, 13
      - serum liver tests, 14
    - static, 16
    - synthetic function tests
      - albumin, 12–13
      - bilirubin, 12
      - prothrombin, 13
  - Liver transplantation, 292
    - immediate postoperative care
      - abdominal evaluation, 273
      - allograft function, 274–275
      - analgesia, 273
      - clinical pathways and protocols, 274
      - electrocardiogram, 273
      - family discussion, 274
      - hemodynamics, 272
      - interdisciplinary discussion, 274
      - laboratory analyses, 274
      - neurologic assessment, 273
      - neuromuscular blockade, 272
      - respiratory status, 272
      - sedation, 273
      - temperature management, 273
      - urine output, 273
    - intraoperative management
      - anesthesia, 270–271
      - arterial catheters, 271
      - ASA monitors, 271
      - cell saver autotransfusion, 271
      - fluid maintenance, 271
      - oximetric PACs, 271
      - peripheral venous catheters, 271
      - phases, 270, 271
      - support team, 270
      - surgical team, 270
      - transesophageal echocardiography, 271
      - vascular access, 271
      - volatile-anesthetic-induced vasodilation, 271
    - postoperative management Postoperative management, liver
  - Living donor liver transplantation (LDLT), 269, 284
  - L-ornithine L-aspartate (LOLA), 94–95
  - Low molecular weight heparin (LMWH), 244
  - Lung compliance
    - abdominal distention, 36
    - anasarca, 37
    - elastance, 35
    - elastic recoil forces, 36
    - expiratory flow, 36
    - FVC measurement, 36
    - hepatic hydrothorax, 37
    - interstitial pulmonary edema, 37
    - intra-abdominal pressure, 36
    - large volume paracentesis, 36
    - lung hysteresis, 36
    - multiple resistive forces, 35
    - PEEP<sub>i</sub>, 36
    - pleural pressure, 36
    - positive pressure mechanical ventilation, 36
    - static compliance, 35
    - transdiaphragmatic pressure, 36
    - volume-pressure relationship, 35
  - Lymphocytes, 9
- ## M
- Macitentan, 219
  - Macroaggregated albumin (MAA), 141
  - Malnutrition, 180
  - Mean arterial pressure (MAP), 49
  - Mean pulmonary artery pressure (MPAP), 115
  - Mechanical ventilation, 144–145
  - Metabolic acidosis, 56
  - Metabolic syndrome, 180
  - Metoclopramide, 221
  - Metoprolol, 217
  - Metronidazole, 92–95
  - Micronutrients, 182
  - Microparticle tissue factor (MPTF), 174, 175
  - Microsomal function, 202
  - Mitochondrial function, 202
  - Model for End stage Liver Disease (MELD) score, 15, 16, 76, 79, 126, 202, 213, 235, 256, 270
  - Modified diet in renal disease (MDRD), 155



Molecular adsorbent recirculation system (MARS), 94, 158, 159, 206, 224  
 ACLF, 293–294  
 albumin circuit, 293  
 ALF, 294  
 blood circuit, 293  
 classic “renal” circuit, 293  
 inflammatory profile, 294  
 Monoethylglycincylidide (MEGX) test, 302  
 Multiple organ dysfunction syndrome (MODS), 222, 302

## N

National Trauma Data Bank (NTDB) analysis, 240  
 Natural killer T (NKT) cells, 9  
 Neomycin, 92–95  
 Nephrotoxins, 159  
 Nervous system, 279  
 Neuraxial anesthesia, 260  
 Neuraxial techniques, 284  
 Neurology  
   analgesics  
     acetaminophen, 214  
     anticonvulsants, 215  
     monitoring, 214  
     NSAID, 215  
     opioids, 214–215  
     tramadol, 215  
   antiepileptic drug, 216–217  
   management, 213  
   neurologic derangements, 213  
   psychiatric and seizure medications, 214  
   safety and efficacy, 213  
   sedatives, 214  
     benzodiazepine, 216  
     dexmedetomidine, 216  
     propofol, 215  
     therapeutic goals, 215  
 Neuronal nitric oxide synthase (nNOS), 88  
 Neutrophil gelatinase-associated lipocalin (NGAL), 47, 156, 157  
 Nicardipine, 218  
 Nitric oxide (NO), 27, 28  
 Nitric oxide-mediated vasodilation, 55  
 Nitrous oxide, 47–48  
 N-Methyl-D-aspartic acid (NMDA) receptor blockade, 215  
 Non acetaminophen-induced ALF, 77  
 Non-alcoholic fatty liver disease (NAFLD), 78  
 Non-alcoholic steatohepatitis (NASH), 169, 223  
 Non-anion gap metabolic acidosis, 56  
 Non-cirrhotic cardiac dysfunction, 29  
 Non-invasive ventilatory support, 277  
 Non-operative management (NOM)  
   advantages, 243  
   altered mental status, 243  
   management, 243  
   mortality, 242  
   outcomes, 243–244  
   Ruscitation outcomes consortium, 243  
   solid organ injury, 242  
 Non-steroidal anti-inflammatory drugs (NSAIDs), 215  
 Norepinephrine, 217  
 Normal liver physiology, 46  
   important functions, 46  
   physiologic functions, 45  
   portal circulation, 46  
   portal hypertension Portal hypertension  
 NT-pro BNP, 26  
 5' Nucleotidase (5'NTD), 13

Numeric Pain Score (NPS), 214  
 Nutrition delivery  
   branched chain amino acids, 184  
   enteral nutrition, 183  
   oral diet, 183  
   parenteral nutrition, 183, 184

## O

Octreotide, 125  
 Omeprazole, 220  
 Ondansetron, 221  
 Opioids, 214  
 Oral treprostnil, 219  
 Organic cation transporter gene (OCTN2), 93  
 Orthotopic liver transplant (OLT), 186

## P

Pantoprazole, 220  
 Paracentesis, 144  
 Parenteral nutrition (PN), 183, 184  
 Pentoxifylline, 140  
 Peritoneal inflammatory syndrome, 247  
 Phase II conjugative metabolism, 213  
 Phenytoin, 217  
 Phosphodiesterase inhibitors, 219  
 Phospholipids, 7  
 Phosphorylation, 55  
 Plasma BNP, 26  
 Pleuroperitoneal communications, 141  
 Plexus of Petren, 127  
 Pneumonia, 195  
 Polyethylene glycol (PEG), 92  
 Polyfactorial, 153  
 Portal circulation, 5  
 Portal hypertension, 46  
   bleeding risk, 263  
   cardiac disease, 23, 114  
   cirrhosis, 121  
   early cirrhosis, 23  
   flow in acinus, 22  
   hemodynamic processes, 121  
   hemodynamics, 47  
   hepatic acinus, 22  
   hepatic venous pressure gradient, 22  
   HVPG, 121  
   hyperdynamic circulation, 48  
   inferior vena cava pressure, 121  
   intrahepatic resistance, 121  
   Kupffer cells, 22  
   late cirrhosis, 23  
   liver cirrhosis, 22  
   multiple pathophysiological mechanisms, 22  
   portosystemic collaterals, 121  
   preoperative decompression, 258  
   progressive vasodilation, 22  
   splanchnic blood flow, 22, 47, 48  
   variceal bleeding Portal hypertensive gastrointestinal bleeding  
 Portal hypertensive gastrointestinal bleeding  
   airway protection, 124  
   bacterial infections and antibiotic prophylaxis, 124–125  
   differential diagnosis, 122  
   endoscopy  
     balloon tamponade, 126  
     EVL and EVS, 125  
     TIPS, 125–126

- Portal hypertensive gastrointestinal bleeding (*cont.*)
  - epidemiology, 122
  - management, acute phase, 124
  - principal complications, 124
  - PVT Portal vein thrombosis (PVT)
  - renal failure, 125
  - restricted resuscitation, 124
  - rFVIIa, 124
  - risk stratification
    - Child Pugh classification, 124
    - endoscopic evaluation, 122
    - esophageal varices and gastric varices, 123
    - IGV1, 123
    - IGV2, 123
    - prediction factors, 122
    - quantitative size estimation, 122
    - rupture risk, 123
    - Sarin classification, 123
    - semi-quantitative morphological assessment, 122
    - stigmata, 123
    - variceal pressure measurement, 124
  - vasoactive medications, 125
- Portal hypertensive gastropathy, 261
- Portal vein embolization (PVE), 202, 236
- Portal vein thrombosis (PVT)
  - activated factor Xa, 129
  - acute
    - anticoagulation, 130
    - cavernous transformation, 127
    - vs. chronic PVT, 126
    - initial compensatory arterial rescue, 127
    - ischemic hepatitis, 127
    - longer-term complications, 127
    - secondary compensatory venous rescue, 127
  - aggressive infusion, 130
  - algorithm, 130, 131
  - anticoagulation, 129–130
  - cavernous transformation, 127
  - chronic
    - vs. acute, 126
    - cavernous transformation, 126
  - cirrhosis presence, 127
  - classification system, 126, 127
  - HCC, 126
  - inherited prothrombotic states, 126
  - management
    - antibiotic management, 128
    - anticoagulation, 128
    - endoscopic retrograde cholangiopancreatography, 128
    - esophageal varices, 129
    - esophagogastroduodenoscopy, 129
    - heparin, 129
    - LMWH, 129
    - primary goal, 128
    - secondary goals, 128
    - VKA, 129
  - presentation and diagnosis, 127–128
  - risk factors, 127
  - SMV, 126
  - TIPS, 130
- Portopulmonary hypertension (POPH), 115, 144, 257, 278
  - case examination, 145
  - clinical manifestations, 145
  - diagnosis, 146
  - epidemiology, 145
  - pathogenesis, 145–146
  - pulmonary artery pressure elevation, 145
  - treatment
    - anticoagulation, 146
    - atrial fibrillation, 146
    - beta blockers, 146
    - Bosentan, 147
    - calcium channel blockers, 146
    - ERA Macitentan, 147
    - goals, 146
    - IV fluids resuscitation, 147
    - liver transplantation, 147
    - MELD exception, 147
    - oral prostanoid, 147
    - PCWP, 146
    - prostanoids, 147
    - pulmonary vasodilators, 146, 147
    - PVR, 146
    - selexipag, 147
    - subcutaneous prostanoids, 147
    - volume status management, 146
- Portosystemic shunts, 107, 146
  - embolization, 92–94
- Positive end-expiratory pressure (PEEP), 41
- Post-hepatectomy hemorrhage
  - bleeding, 238
  - clinical examination, 238
  - hemorrhage control, 238
  - incidence, 238
  - ISGLS, 238
  - patient factors, 238
  - resuscitation, 238
  - standard coagulation tests, 238
  - TEG, 238
- Post-hepatectomy hepatic insufficiency, 239
- Postoperative management, liver
  - ALF, 284
  - cardiac considerations
    - apical ballooning, 279
    - atrial arrhythmias, 279
    - disease severity, 278
    - dobutamine, 279
    - DSE, 278
    - fluid administration, 279
    - hyperdynamic circulation, 278
    - Mercedes incision, 279
    - NE/epinephrine, 279
    - postoperative hypertension, 279
    - post-transplant dilated cardiomyopathy, 279
    - resting and stress echocardiography, 278
    - restrictive cardiomyopathy, 278
    - screening process, 278
    - vasodilation-associated hyperdynamic circulation, 278
    - vasopressin, 279
  - coagulation management, 282
  - complications
    - biliary, 284
    - hemorrhage, 283
    - thrombosis, 283
    - vascular, 283
    - wound, 284
- ICU discharge, 284
- ICU readmission, 284
- immunosuppression, 282–283
- infectious disease, 283
- LDLT, 284
- marginal/extended criteria donors, 284
- metabolic considerations
  - adrenal function, 281
  - glycemic control, 281
  - nutrition, 281

- relative adrenal insufficiency, 281
  - steroid bolus administration, 281
  - nervous system, 279–280
  - renal considerations
    - beta-2 agonists, 280
    - biopsy, 281
    - CRRT, 280
    - dialysis assessment, 280
    - hepatic allograft, 280, 281
    - HRS, 280
    - intraoperative hyperkalemia, 280
    - potassium-depleted red cells, 280
    - renal replacement therapy, 281
    - sodium bicarbonate, 280
  - respiratory considerations
    - ARDS, 277
    - delayed extubation, 275
    - early extubation, 275–277
    - fast track/rapid recovery pathway, 275
    - HPS, 278
    - immediate extubation, 275
    - non-invasive ventilatory support, 277
    - PPH, 278
    - prompt extubation, 275
    - pulmonary edema, 277
    - VAP, 278
    - ventilator weaning protocol, 275, 276
  - Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, 242
  - Primary biliary cirrhosis (PBC), 78
  - Primary sclerosing cholangitis (PSC), 78
  - Pro-coagulation factors, 8
  - Prometheus, 158, 159, 224
  - Propofol, 215, 273
  - Propofol infusion syndrome (PRIS), 216
  - Prostacyclin (PGI<sub>2</sub>), 28, 146
  - Protein metabolism, 8, 300
  - Prothrombin, 13
  - Prothrombin complex concentrates (PCC), 259
  - Proton pump inhibitors (PPIs)
    - esomeprazole, 220
    - lansoprazole, 220
    - omeprazole, 220
    - pantoprazole, 220
  - Pulmonary disease
    - endothelin receptor antagonists, 219–220
    - phosphodiesterase inhibitors, 219
    - synthetic prostacyclins, 218
  - Pulmonary edema, 277
  - Pulmonary embolism (PE), 244
  - Pulmonary function tests, 33, 37, 38
  - PVT Portal vein thrombosis (PVT)
  - Pylephlebitis, 128
- R**
- Rebalanced hemostasis
    - ALF, 168
      - maximum blood clot strength, 173
      - microparticles, 174
      - MPTF, 174, 175
      - platelet aggregation, 173
      - thromboelastography, 172, 173
      - whole blood clot lysis, 175
    - chronic liver disease, 165–168
  - Recombinant human factor VIIa (rFVIIa), 124
  - Refractory acutely bleeding varices, 261
  - Refractory ascites, 261
  - Refractory hepatic hydrothorax, 261
  - Relative adrenal insufficiency (RAI), 224
  - Renal dosing adjustments, 220
  - Renal hypoperfusion, 50
  - Renal physiology
    - acid-base disorders
      - ketoacidosis, 56
      - lactic acidosis, 56
      - non-anion gap metabolic acidosis, 56–57
      - treatment, 57
    - acute liver failure, 53
    - antidiuretic hormone and water balance, 55
    - chronic liver disease, 54
    - cirrhosis-induced changes, kidney, 54
    - non-vasomotor effects
      - bile cast nephropathy, 57
      - inflammatory changes, 57
      - intra-abdominal hypertension, 57
    - sodium and water homeostasis
      - ADH, 55
      - ascites formation, 56
      - hypervolemic/dilutional hyponatremia, 55, 56
      - hyponatremia, 56
    - systemic hemodynamic changes, 54
    - vasodilation, 55
  - Renal replacement therapy (RRT), 158, 281
  - Renal tubular acidosis, 57
  - Renal vasoconstriction system, 50
  - Respiratory mechanics, 35, 41
  - Respiratory physiology
    - acid-base neutrality, 37–38
    - ARDS Acute respiratory distress syndrome (ARDS)
      - clinical assessment
        - expiratory reserve volume, 32
        - functional residual capacity, 32
        - obstruction and restriction, 33
        - residual volume, 32
        - slow vital capacity, 32
        - spirometric patterns, 33
        - total lung capacity, 32
        - vital capacity, 32
      - DLCO, 38
      - neuromuscular strength and exercise tolerance, 37
      - respiratory system compliance Lung compliance
      - V-Q matching, 38
  - Resuscitation outcomes consortium, 243
  - Reticuloendothelial system (RES), 107, 139
  - Richmond agitation sedation scale (RASS), 215, 273
  - Rifaximin, 92–95
  - Right heart catheterization, 146
  - Rose Bengal test, 16
  - Rotational thromboelastometry (ROTEM), 242
- S**
- Sarcopenia, 181
    - aerobic and resistance activity, 185
    - Child-Pugh scores, 185
    - D'Amico stage classification, 185
    - leucine-rich supplements, 185
    - mechanisms, 185
    - MELD scores, 185
    - vs. non-sarcopenic group, 185
    - and liver transplant, 186
    - obesity, 185
    - therapeutic options, 185
    - transjugular intrahepatic portosystemic shunt, 185
  - Sedation agitation scale (SAS), 215

## Sedatives

- benzodiazepine, 216
- dexmedetomidine, 215–216
- propofol, 215–216
- therapeutic goals, 215

## Seizures, 100

## Sepsis

- definition, 204
- hepatocellular events, 204
- injury pattern, 205
- mortality, 204
- organ dysfunction and failure, 204

## Sequential organ failure assessment (SOFA), 202, 222, 302

## Serum aminotransferase, 111

## Serum creatinine (sCr), 154, 155, 158

## Serum glutamic oxalo-acetic transaminase (SGOT) Aspartate transferase (AST)

## Serum glutamic pyruvic transaminases (SGPT) Alanine transferase (ALT)

## Severe acute malnutrition (SAM), 180

## Shock liver Ischemic hepatitis

## Sildenafil, 219

## Simultaneous liver kidney (SLK), 159

## Single-pass albumin dialysis (SPAD), 224, 295

## Skin and soft tissue infections (SSTIs), 195

## Somatostatin analogues, 125

## Spirometry, 32

## Splanchnic blood flow, 146

## Splanchnic vasodilation, 49

## Spontaneous bacterial empyema Spontaneous bacterial pleuritis (SBPL)

## Spontaneous bacterial peritonitis (SBP), 49, 50, 154

- antibiotic prophylaxis, 194
- cirrhotic ascites, 192
- definition, 192
- diagnosis, 193
- management, 194
- microbiology, 192–193
- presentation, 192
- prevention, 194–195
- risk factors, 192

## Spontaneous bacterial pleuritis (SBPL)

- chest tube placement, 143
- clinical manifestation and diagnosis, 143
- mechanisms, 142
- pleural complication of cirrhosis, 142
- prophylactic antibiotic therapy, 143
- third-generation cephalosporin, 143

## Static test

- bilirubin, 300
- enzymes, 301
- hepatocellular synthetic function, 301
- pros, 300

## Stress ulcer prophylaxis, 220

## Superior mesenteric vein (SMV), 126

## Sympathetic nervous system, 50

## Synthetic prostacyclins, 218

## Systemic inflammatory responses syndrome (SIRS), 46, 164

## Systemic vascular resistance (SVR), 49

## Systemic vasoconstrictive systems, 55

## T

## Tadalafil, 219

## Terlipressin, 125, 157, 158

## Therapeutic hypothermia, 94–95

## Thoraco-abdominal compliance, 143

## ascites Ascites

## clinical setting, 143

## IAP Intra-abdominal pressure (IAP)

## Thrombin generation

- with cirrhosis and normal healthy controls, 166
- pathways, 165

## Thromboelastography (TEG), 167, 168, 172, 238, 242

## Thyroid, 223

## Total intravenous anesthetic (TIVA), 271

## Transaminases Aminotransferases

## Transcranial Doppler ultrasound (TCD), 99

## Transferrin, 8

## Transfusion-associated volume overload (TACO), 259

## Transfusion-related acute lung injury (TRALI), 259

## Transfusion-related circulatory overload (TACO), 259

## Transfusion Requirements in Critical Care (TRICC) trial, 242

## Transjugular intrahepatic portosystemic shunt (TIPS), 26, 114, 115, 185, 212, 261

## ascites, 261

## contraindications, 256

## hepatic hydrothorax, 142

## HRS, 158

## indications, 261

## MELD score, 261

## portal decompression, 261

## portal hypertensive gastrointestinal bleeding, 125

## systematic workup, 261

## Transthoracic echocardiography (TTE) plus bubble study, 261

## Treprostinil, 218

## Tricyclic antidepressants (TCA), 215

## Triglycerides, 7

## Troponins, 111

Tumor necrosis factor alpha (TNF- $\alpha$ ), 28

## Type C hepatic encephalopathy

- brain imaging, 89–90
- cerebral edema and mortality, 84
- clinical features, 91
- plasma ammonia lowering strategies
  - alternative pathway therapy, 94
  - ammonia lowering antibiotics, 92–93
  - lactulose and lactitol, 92
  - neurotransmitter blockade, 94
  - non-pharmacological interventions, 93–94
  - nutritional and micronutrient supplementation, 93
- PEG, 92
- surgical treatment, 94–95
- precipitating factors, 90, 91

## Type I hepatorenal syndrome, 260

## U

## UDP-glucuronyl transferase, 12

## Urinary tract infection (UTI), 195–196

## V

## Variceal bleeding, 121 Portal hypertensive gastrointestinal bleeding

## Variceal hemorrhage, 48, 49

## Varices

- gastroesophageal varices, 48
- HPVG, 48
- portosystemic collaterals, 48
- variceal hemorrhage, 48, 49

## Vasoactive substances, 139



- Vasoconstrictor therapies, 54, 157, 158
    - norepinephrine
      - midodrine, 158
      - octreotide, 158
      - vs. terlipressin, 158
    - vasopressin analogues
      - renal afferent vasodilatation, 157
      - renin-angiotensin system, 157
      - sympathetic nervous system, 157
      - terlipressin, 157
      - vasoconstrictive effect, 157
  - Vasopressors, 217
  - Venous thromboembolism (VTE) prophylaxis, 169, 221, 244, 245
  - Ventilation-perfusion (V/Q) mismatch, 138
  - Ventilator-associated pneumonia (VAP), 278
  - Ventricular systolic function, 23
  - Viral infections
    - chronic liver disease
      - HAV, 196–197
      - HBV/HCV, 197
      - HDV, 197
      - HEV, 197
      - HIV, 197–198
      - influenza virus, 198
  - Viscoelastic tests, 258, 260
  - Visual analogue scale (VAS), 214
  - Vitamin K antagonist warfarin, 129–130
  - von Willebrand factor (VWF), 259
  - V-Q matching, 38–40
- W**
- World Society of the Abdominal Compartment Syndrome (WSACS), 131
- Z**
- Zinc, 92–95